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THE RELATIVE MERITS OF ENCEPHALOGRAPHY AND VENTRICULOGRAPHY FOR THE INVESTIGATION OF INTRACRANIAL TUMOURS

BY

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The view was formerly held, and still is in many centres, that encephalography should not be used in cases where the intracranial pressure is raised or if a posterior fossa tumour is suspected. Several authors prefer ventriculography to encephalography in all cases where the clinical signs and symptoms indicate a brain tumour. The main reason for this seems to be that the risk of coning after the procedure is considered to be high. Using the old technique, which means that a large amount of fluid is drained before gas is injected, this risk must be considerable, especially if there should be a block at the foramen of Magendie, for example.

In recent times, however, a technique, based on the principle that the pressure should be maintained as well as possible (Lindgren, 1949, 1950, 1951, 1954; Robertson, 1941, 1946, and others), has been introduced. The technique, described by Lindgren seems to be the one which is most satisfactory in that respect. According to Lindgren, only a few drops of fluid (enough to make sure that the needle is in the right position) should be allowed to escape before gas is injected. The fluid-gas exchange is performed in fractions of 5 to 10 ml., the gas always being injected before the same amount or somewhat less fluid is withdrawn. If the intracranial pressure is raised practically no fluid is allowed to escape, at least not until gas is seen to enter the ventricular system. In this way the risks of coning must be greatly diminished.

It is well known that ventriculography is not free from risks. The pressure conditions may be considerably altered causing herniation. Also the brain puncture itself may cause damage to the brain substance. Zülch, Hirnödem, Hirnschwellung, and Hirndruck (1951) have demonstrated oedema along the track of the needle and calcification can often be seen further along this track (Falk, 1951, 1953). Sometimes the puncture, especially if difficult, may cause more severe damage in the form of haemorrhages and malacia.

When deciding which method of examination should be used, not only the risks involved in the method should be considered but also the information that can be gained from it. Provided the C.S.F. pathways are free and ventricular filling can be obtained at encephalography, this method allows a more complete examination than does ventriculography, as the cisterns can also be studied. This is of special value in cases with basal extracerebral tumours. These tumours as a rule can be outlined by gas in the cisterns (Figs. 1, 2, and 3). Extracerebral tumours which are too small to cause any deformity of the ventricular system cannot be demonstrated at all by means of ventriculography. Falk also points out that gas sometimes passes more easily from the third ventricle through the foramen of Monro than in the opposite direction. Thus, for example, in cases where the anterior part of the third ventricle is compressed by a large suprasellar tumour it may be impossible to fill the third ventricle at ventriculography. At encephalography it should always be possible to make a correct diagnosis in tumours of this kind.

Using a correct technique an adequate filling of the ventricular system can be obtained in more than 95% of cases, provided the pathways are not obliterated. The aqueduct and fourth ventricle can be studied more easily and accurately at encephalography in the sitting position, when gas passes into the ventricles, than at ventriculography. At the latter examination pictures have to be taken when gas passes from the ventricular system into the cisterna magna. The gas may then disappear before the pictures are taken. If, on the other hand, the C.S.F. pathways are obliterated, ventriculography is necessary for examination of the ventricular system. Even in these cases, however, encephalography may provide valuable information. If the tumour is outlined by gas in the cisterns examination of the ventricles is as a rule not necessary (Fig 3).

In cases where the block is situated in the aqueduct

FIG. 1.—Acoustic neurinoma on the left side. Cerebellopontine cistern is displaced medially and outlines the tumour. Small indentation in the fourth ventricle from the left and below. Ventricular system otherwise normal.

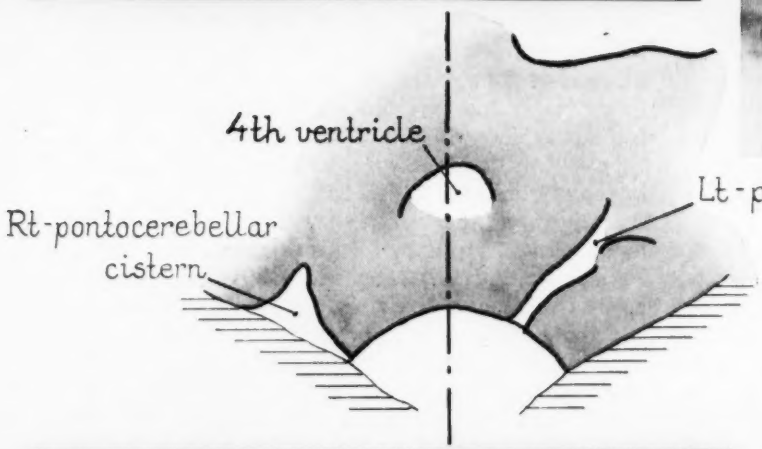
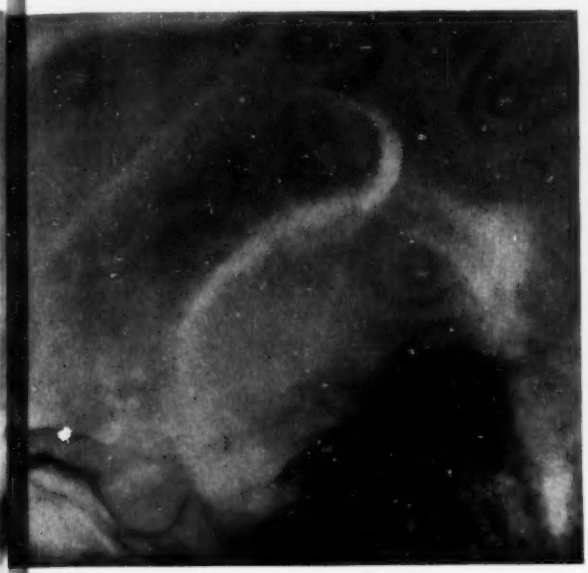


Fig. 1

FIG. 2.—Meningioma from the sphenoidal plane outlined by cisternal gas. Slight bulging from below in the anterior horns.

Fig. 2

FIG. 3.—Large meningioma on the right side mainly arising from the tentorium. The tumour is outlined by cisternal gas and can be exactly localized in spite of the fact that no ventricular filling is obtained.



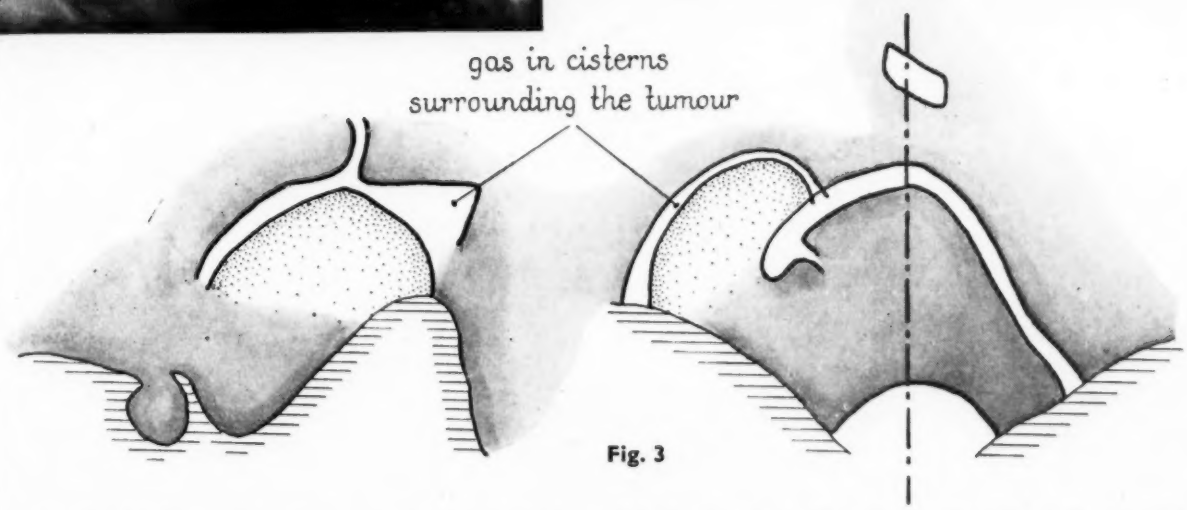


Fig. 3

or in the third ventricle, the part of the ventricular system below the block may be filled at encephalography, thus allowing a more accurate diagnosis to be made (Figs. 4 and 5). Herniation of the tonsils can be directly seen at encephalography and tentorial herniations also may cause characteristic changes in the cisterns. If the vallecula is filled with air and is seen to be displaced to one side or the other, this indicates that there is an expanding process in the contralateral part of the posterior fossa (Fig. 6).

In recent years several cases and series of cases have been reported where this modern technique has been used also in posterior fossa tumours and in cases where the intracranial pressure is raised (Lindgren, 1951; Falk, 1953; Ruggiero, David, and Talairach, 1955; David, Ruggiero, and Talairach, 1954; Ruggiero, 1956; Robertson, 1941, 1946; Dressler and Albrecht, 1956; Sheldon, Wickbom, and Pennybacker, 1953; Wickbom and Sheldon, 1953) among many others. Falk, in his series of 195 tumour cases (including 37 tumours in the posterior fossa) examined by encephalography, reported no ventricular filling in 24 cases (eight supra- and 16 infratentorial tumours). In six cases attacks of herniation occurred after the procedure. In only one of them, a pontine glioma for which ventriculography was also performed, was the result fatal. Ruggiero *et al.* (1955) reported four accidents in 40 cases of brain tumour where encephalography

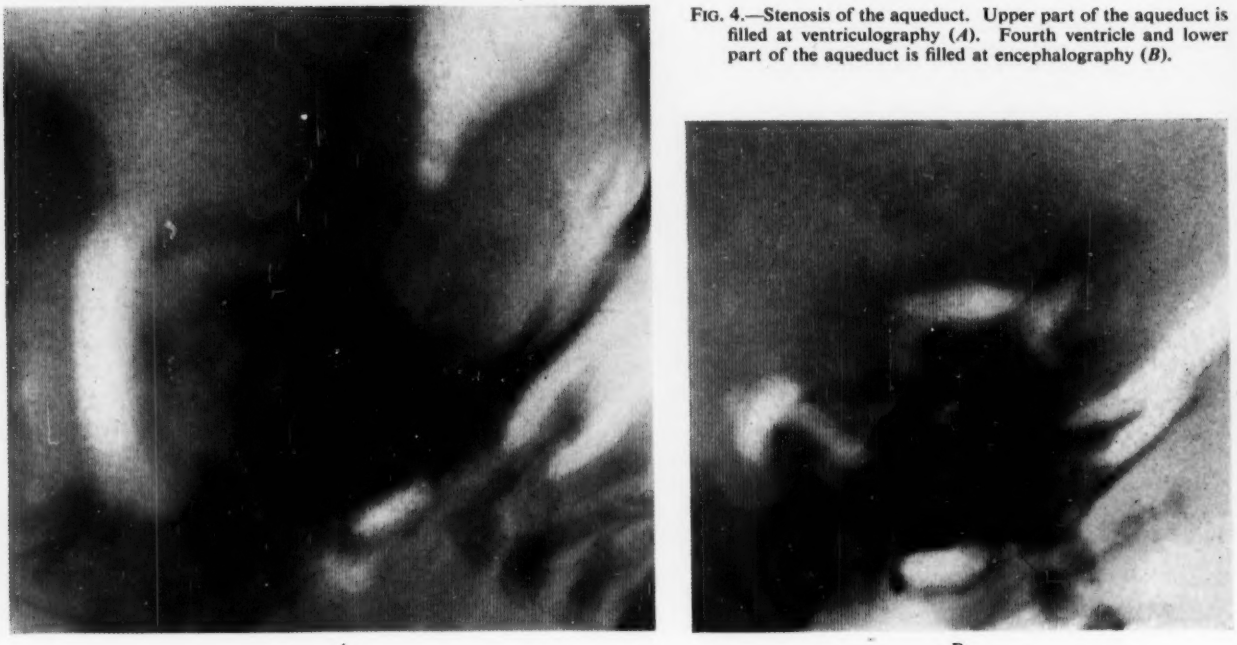


FIG. 4.—Stenosis of the aqueduct. Upper part of the aqueduct is filled at ventriculography (*A*). Fourth ventricle and lower part of the aqueduct is filled at encephalography (*B*).

A *B*

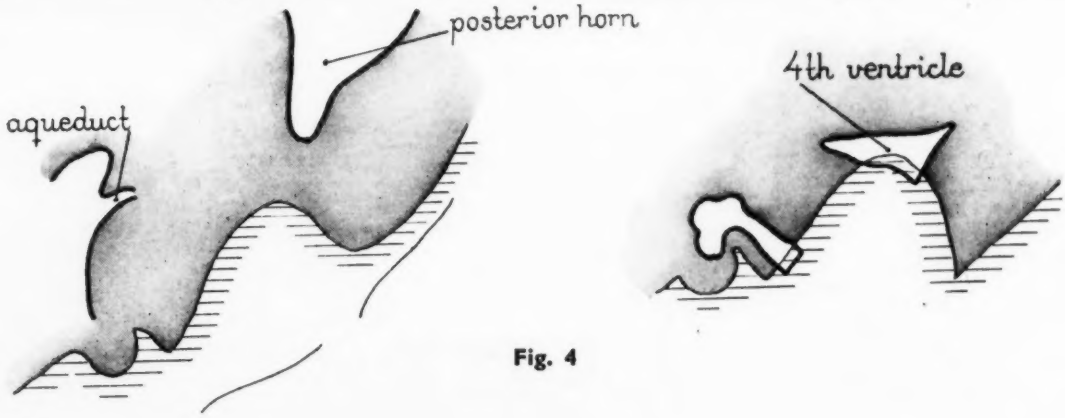


Fig. 4

was performed and in four out of 23 cases where ventriculography was used. One of the former and three of the latter were fatal. Dressler and Albrecht (1956) reported deterioration of the patient after encephalography in two cases (1·2%) of supratentorial and in three cases (11%) of posterior fossa tumour. The corresponding figures for ventriculography were 21 (16%) and eight cases (13%) respectively. Falk, as well as Ruggiero *et al.*, used the lumbar route and Dressler and Albrecht cisternal puncture for the insufflation of gas. The motive for using cisternal puncture should be that in this way cases with herniation of the tonsils will be automatically excluded. Dressler and Albrecht are of the opinion that in these cases no ventricular filling can be obtained at encephalography. This is not always true (Fig. 6) and, furthermore, important information may be gained from an encephalographic study even if no ventricular filling is obtained (Figs. 7 and 3).

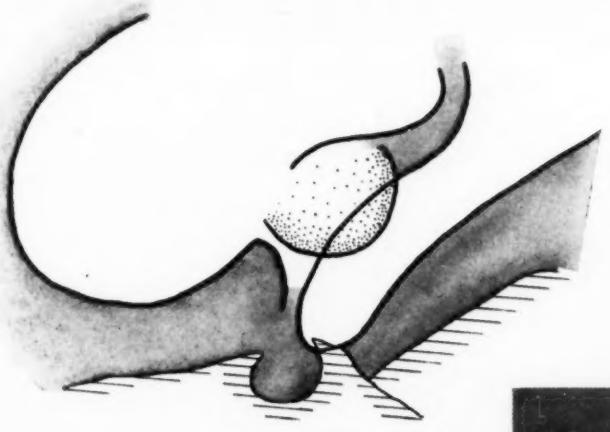
Judging from these reports it seems as if encephalography performed in this way should involve no more risks than does ventriculography. This is also in accordance with our own experience which dates from the time when we worked at the Serafimer Hospital in Stockholm. In the reports hitherto published the material seems to be in some measure selected. Thus ventriculography has been performed in some of the cases without a preceding attempt to fill the ventricles by means of encephalography. Dressler and Albrecht state that in their cases encephalography was always performed before

FIG. 5.—Colloid cyst of the foramen of Monro.
A. Ventriculography: upper part of the cyst is visualized.
B. Encephalography: lower part of the cyst is outlined by gas in the posterior part of the third ventricle.

A

B

Fig. 5



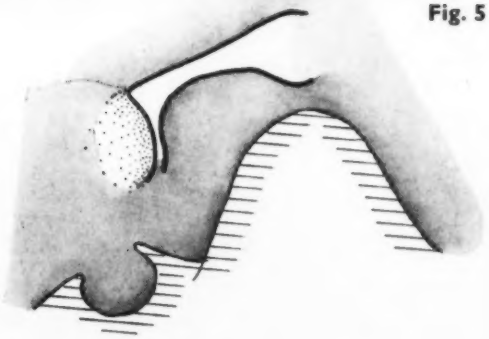


FIG. 6.—Meningioma over the left cerebellar hemisphere. Gas enters the ventricular system in spite of herniated tonsils (seen on the picture). Marked kink of the aqueduct.

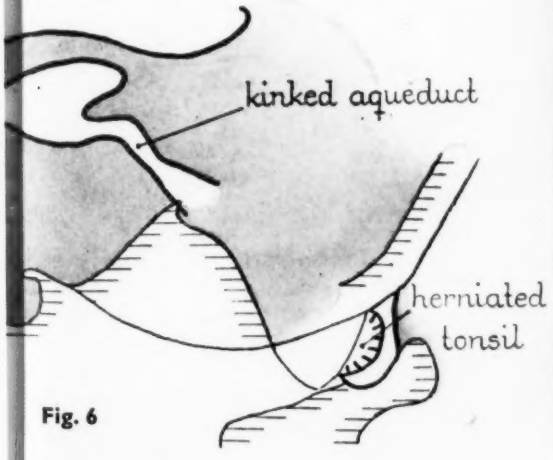


Fig. 6

A

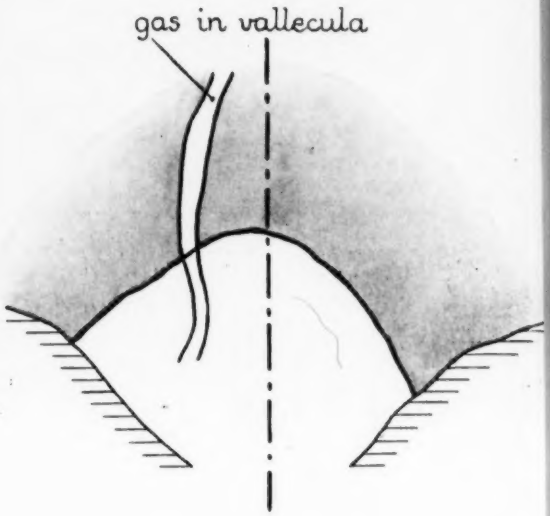
B

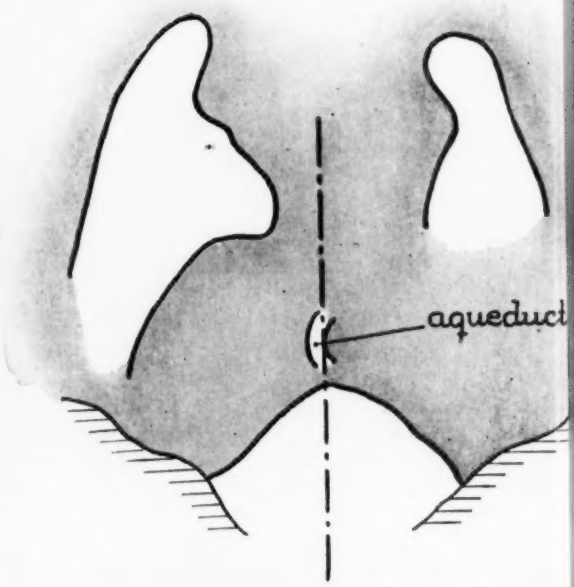
Fig 7

FIG. 7.—Tumour in the left cerebellar hemisphere.

A. Encephalography: gas is seen in the vallecula, which is displaced to the right, indicating a tumour to the left in the posterior fossa.

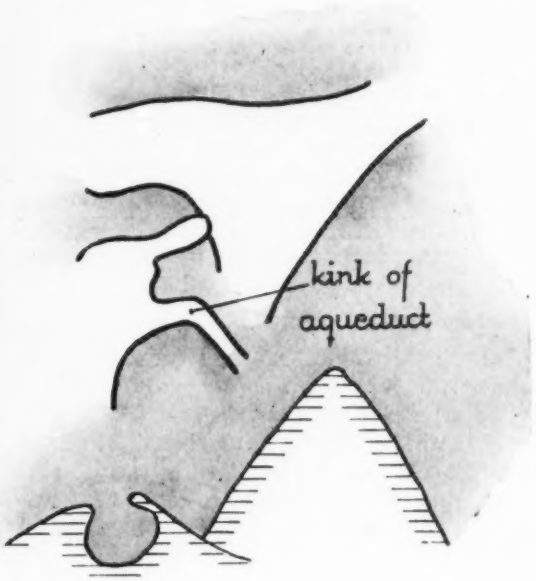
B-C. Ventriculography: marked kink of the aqueduct, indicating a tumour in the dorsal part of the posterior fossa but no definite shift.





C

Fig. 7



ventriculography. In their material, however, encephalography was performed in 27 cases of infra- and in 166 cases of supratentorial tumour. The corresponding figures for ventriculography were 61 and 128 cases respectively. These figures seem to indicate either that encephalography failed to give an accurate diagnosis in a much higher percentage of cases than in our material, or, that in fact only ventriculography had been performed in some of the cases. One explanation of the comparatively high figures for ventriculographies in their material may be that no fluid was obtained at cisternal puncture in several cases. They give no figures as to the diagnostic value of the encephalographic examination.

To form a true opinion of the risks involved and the informative value of the methods, it seems necessary to have a material which is not selected, *i.e.*, which is uniformly treated. From such a material it could be expected that more definite conclusions could be drawn. In that way it might perhaps also be possible to select a certain group of tumours where encephalography is less likely to give enough information and make ventriculography the investigation of choice.

In order to obtain such a series the following principles have been followed ever since the neurosurgical department at Sahlgrens Hospital was started in May, 1953. In all cases where an air study is indicated an attempt is first made to fill the ventricles by the lumbar route. If this fails and if the appearance of the cisterns does not permit of an accurate diagnosis, this examination is followed by ventriculography. In cases where there is evidence of increased pressure or signs indicating a herniation, burr holes are made beforehand. In this way encephalography can be followed directly by ventriculography and ventricular puncture can if necessary be performed at once. The examination is performed by the radiologist but the neurosurgeon can be called immediately if complications of any kind should occur.

For encephalography the technique worked out by Lindgren is used. As a rule the lumbar route is used, thus allowing a freer handling of the patient's head and injection of gas even if the cisterna magna is compressed by herniated tonsils. An air study has as a rule been considered indicated if (1) a lesion in one of the cerebral hemispheres is suspected and carotid angiography appears normal or fails to give all information wanted concerning the extent and true nature of the lesion ; (2) in cases where the clinical picture indicates the presence of an intracranial lesion but signs from the cerebral hemispheres are lacking ; (3) cases where the clinical signs indicate a lesion in the posterior fossa.

These are only general rules. For example, in some cases of vascular tumour in the posterior fossa a correct diagnosis has been obtained at vertebral angiography and accordingly an air study has not been necessary.

TABLE I

TYPES OF TUMOUR DIAGNOSED IN THE WHOLE SERIES

Glioma	162
Meningioma	61
Pituitary adenoma	32
Metastatic tumour	28
Neurinoma	24
Craniopharyngeoma	7
Cerebellar angioma	7
Dermoid	2
Colloid cyst	1
Cholesteatoma	1
Tuberculoma	1
Chordoma	1
Total	327

TABLE II

LOCALIZATION OF TUMOURS IN WHOLE SERIES

Supratentorial tumours	250
Suprasellar tumours	45
Supratentorial tumours (suprasellar excluded)	205
Gliomas	132
Meningiomas	50
Metastatic tumours	20
Colloid cyst	1
Neurinoma	1
Dermoid	1
Infratentorial tumours	75
Cerebello-pontine angle tumours	29
Cerebellar tumours	36
Gliomas	17
Meningiomas	2
Metastatic tumours	8
Angiomas	7
Tuberculoma	1
Dermoid	1
Gliomas of the pons	8
Stenosis of the Sylvian aqueduct	2
Pinealomas	2
Total	327

Results in Present Series

Table I illustrates the total tumour material of the clinic in all 327 cases. Two cases of stenosis of the Sylvian aqueduct are grouped together with the gliomas; one of the cases was actually a very small glioma which occluded the aqueduct. In the second case no pathological verification was obtained.

In Table II the material is divided into different groups according to the localization of the tumour. The suprasellar tumours are separated into a special group. The infratentorial tumours are divided into four different groups. One consists of the cerebello-pontine angle tumours, neurinomas and meningiomas, in which group the tumours of the clivus, two meningiomas and one chordoma, are included. Another two meningiomas of the posterior fossa were localized to the convexity of the cerebellum involving the cerebellar hemispheres, and accordingly grouped together with the cerebellar tumours. Eight gliomas of the pons constitute one group. The fourth group consists of the two cases of stenosis of the Sylvian aqueduct.

Encephalography was performed in 222 cases, ventriculography in 53, and angiography in 236.

Suprasellar Tumours.—There are 45 suprasellar tumours. In one of them choked disks were present. This patient had a very big chromophobe adenoma growing into the left frontal lobe and angiography indicated the presence of a frontal lobe tumour. The encephalographic examination was incomplete, and only a small amount of air entered the ventricular system. The left frontal horn was displaced indicating a tumour, but the examination did not give enough information about the exact extent of the tumour. In two cases only no air entered the ventricular system, but in both the suprasellar tumour was outlined by cisternal air.

This group will not be discussed further because pneumography is as a rule not necessary for the localization of the lesion. Encephalography is recommended if the surgeon wants to visualize the tumour and obtain more accurate information about its extensions.

No complications have occurred and ventriculography was not necessary in this group.

Supratentorial Tumours.—The remaining tumours above the tentorium (205 cases), mainly gliomas and meningiomas, are grouped together, 101 of them presenting with choked disks.

Table III demonstrates the result of the air studies. In the table incomplete air filling means that no air or only a small amount of air, for example, only in one side, had entered the ventricular system. In some cases, for example, in some of the suprasellar and the cerebello-pontine angle tumours, the appearance of the cisterns alone permitted a topographical diagnosis. A positive result means that the ventricular system is adequately filled with air permitting a reliable topographical diagnosis. A negative result means that the examination is complete but appears normal or

TABLE III

SUPRATENTORIAL TUMOURS (SUPRASELLAR TUMOURS EXCLUDED)

Technique Used	Positive		Negative		Tumour Suspected		Incomplete Air-filling		Air in Cisterns Indicating Tumour	
	Choked Disks	No Choked Disks	Choked Disks	No Choked Disks	Choked Disks	No Choked Disks	Choked Disks	No Choked Disks	Choked Disks	No Choked Disks
Encephalography	24	57	2	5	1	2	14	9	—	—
Ventriculography	15	4	—	—	—	—	—	—	—	—

at least does not permit the diagnosis of an expanding lesion. In some cases deformities of the ventricular system have been too small to permit a definite diagnosis of a tumour and these cases have been classified as " tumour suspect ". The ventricular system was incompletely filled with air in 23 cases out of 114 in which encephalography was performed. In only 19 cases had ventriculography to be undertaken. Two of these ventriculograms were not preceded by encephalography. One patient, a 16-month-old girl, had a big glioma in the right ventricle with signs of high pressure. She was in bad condition when referred to the hospital and was operated upon immediately. However, a previous attempt at cisternal puncture had been made and no fluid obtained, thus indicating a herniation of the tonsils. The other patient, a man aged 53 years, was comatose on admission to hospital. A ventriculogram was performed immediately and a left parietal tumour was diagnosed. At operation the same day a malignant glioma was removed.

One of the cases had a colloid cyst at the foramen of Monro and encephalography outlined the posterior part of the tumour in the third ventricle. Only a very small amount of air had entered the lateral ventricles and ventriculography was necessary for complete examination (Fig. 5).

One patient, a case of pterion meningioma with choked disks of 4 diopters, did not tolerate the encephalography. The patient was rather drowsy when the examination was started. After injecting about 5 to 10 ml. air she became comatose and a ventricular puncture was done, together with air injection and ventriculography. The patient was operated on the same day with success.

Another case was of a malignant glioma of the left temporal lobe with choked disks of 7 diopters. Air entered the ventricular system at encephalography very slowly and in a small amount and the patient fainted. The examination was therefore abandoned. The patient recovered in some minutes and a subsequent angiogram revealed the malignant glioma.

Cerebello-pontine Angle Tumours.—Of the posterior fossa tumours, one group is composed of the cerebello-pontine angle tumours and tumours of the clivus, 29 cases in all, including 22 neurinomas, two meningiomas of the cerebello-pontine angle, one papilloma in the cerebello-pontine angle, three meningiomas of the clivus, and one chordoma of the clivus. Twelve of these cases presented with choked discs. Encephalography performed in 22 cases was negative in two (Table IV). One of these cases was the papilloma, in which the air study only demonstrated a symmetrical hydrocephalus. The diagnosis was obtained by vertebral angiography. The second case was an acoustic neurinoma with choked disks of 5 diopters. The patient, a 60-year-old woman, had an atypical history with normal vestibular findings and only slightly diminished hearing on the left side. This was interpreted by the otologists as being caused by local changes after an infection. No changes in the porus could be seen. The case was misinterpreted both from the clinical and radiological points of view. The encephalogram was not tolerated by the patient and ventricular drainage was performed. Three weeks after encephalography the patient was seen by one of us (G. N.) and an operation was performed because the clinical signs and symptoms, in the opinion of the surgeon, definitely indicated a posterior fossa tumour. The operation, however, could not save the life of the patient. In five cases the air study was incomplete in as much as no air entered the ventricular system. In these cases, however, cisternal air outlined the tumour beautifully.

In this group of tumours, as in the suprasellar group, the clinical signs usually, with only few exceptions, were so clear that encephalography was not necessary for the localization of the tumour. If an air study is indicated encephalography should be preferred as it is usually well tolerated and is often more reliable than ventriculography. Ventriculography has not been necessary in this group.

Encephalography was performed in all eight cases of gliomas of the pons (Table V). One of the cases was referred to the hospital in a very advanced state with hemiparesis and difficulties in swallowing, but no choked discs. Encephalography upset this patient but a ventricular tap caused immediate improvement. The patient was not operated upon and died later, death not depending on the en-

TABLE IV
PONTINE ANGLE TUMOURS

Technique Used	Positive		Negative		Tumour Suspected		Incomplete Air-filling		Air in Cisterns Indicating Tumour	
	Choked Disks	No Choked Disks	Choked Disks	No Choked Disks	Choked Disks	No Choked Disks	Choked Disks	No Choked Disks	Choked Disks	No Choked Disks
Encephalography	6	9	2	—	—	—	—	5	—	5
Ventriculography	—	—	—	—	—	—	—	—	—	—

TABLE V
INTRAPONTINE TUMOURS

Technique Used	Positive		Negative		Tumour Suspected		Incomplete Air-filling		Air in Cisterns Indicating Tumour	
	Choked Disks	No Choked Disks	Choked Disks	No Choked Disks	Choked Disks	No Choked Disks	Choked Disks	No Choked Disks	Choked Disks	No Choked Disks
Encephalography	1	2	—	—	—	—	1	4	—	3
Ventriculography	1	4	—	—	—	—	—	—	—	—

cephalography but on the progress of the inoperable lesion. Ventriculography completed the air study in five cases. Sometimes it can be difficult to say whether the displacement of the aqueduct and the fourth ventricle is caused by an intra- or extrapontine tumour. A study of the air in the basal cisterns is then of great value in the differential diagnosis. Encephalography is therefore more informative in this lesion than is ventriculography. In two cases of stenosis or tumour of the Sylvian aqueduct encephalography and ventriculography supplemented each other, demonstrating the exact extent of the lesion (Fig. 4).

Cerebellar Tumours.—The remaining posterior fossa tumours (36 cases) are grouped together as they are localized to the cerebellar hemispheres, vermis, or the fourth ventricle. In 30 cases choked disks were present (Table VI).

Thirty-two encephalograms were performed. In four cases no air study was done, vertebral angiography having given an exact diagnosis in two angiomas and in two metastatic tumours.

Encephalography was performed with sufficient air-filling of the ventricular system to permit an accurate diagnosis in three cases.

In another six cases, where the air had not entered the ventricular system, cisternal air localized the tumour to the correct hemisphere. However, ventriculography had to be performed in 26 cases.

Coning of the tonsils was demonstrated in 16 cases, in spite of which the examination was well tolerated. In only one case the clinical symptoms increased after encephalography with attacks of severe headache, but the condition was never alarming and a ventricular tap was not considered necessary. The patient had a metastasic tumour of the cerebellum and on admission presented with severe headache and stiffness of the neck. There was no papilloedema.

Pinealomas.—In the two cases of pinealoma choked disks of 3 diopters were present. In spite of the localization of the tumour and the increased pressure, encephalography could be performed with success and without complication in one of the cases. In the other case encephalography was not tolerated and the examination had to be interrupted. A ventricular tap was performed followed by air injection and ventriculography. The tumour was later removed with success.

Of the 222 cases in which encephalography was performed, 82 presented with choked disks. The patient's condition deteriorated in six cases only, in four of which papilloedema was present. One of these patients, the case of pinealoma, was in good condition when the examination started, but the other five, including the two cases with no choked disks, were in poor condition. Some were rather drowsy, some had severe headache and stiffness of the neck. A ventricular tap improved the condition in three cases. In one case the examination must be considered to have contributed to the fatal outcome. Curiously enough in this case the encephalography was successful in so far as the gas entered the ventricular system and a blocking of the C.S.F. pathways was not therefore caused by the tumour.

Discussion

In discussing which method should be used, encephalography or ventriculography, some authors claim that encephalography should not be used if the degree of papilloedema exceeds 2 diopters. In

TABLE VI
TUMOURS IN CEREBELLUM OR FOURTH VENTRICLE

Technique Used	Positive		Negative		Tumour Suspected		Incomplete Air-filling		Air in Cisterns Indicating Tumour	
	Choked Disks	No Choked Disks	Choked Disks	No Choked Disks	Choked Disks	No Choked Disks	Choked Disks	No Choked Disks	Choked Disks	No Choked Disks
Encephalography	3	—	—	—	—	—	23	6	5	1
Ventriculography	23	3	—	—	—	—	—	—	—	—

our material this occurred in 35 cases and in only four the encephalogram was not tolerated, but this was also the case in two patients with no papilloedema.

In our opinion a comparison between complications following encephalography and ventriculography must inevitably be difficult. It is almost impossible to get two series of cases which from a clinical point of view are equal enough to permit a fair comparison. When a ventriculogram has been performed the operation is done the same day if the lesion is considered operable. A post-operative death under such circumstances cannot as a rule be attributed to the preceding examination. In 11 cases where ventriculography had demonstrated inoperable lesions death occurred in one only, and even in this case—a glioma of the pons—the death could not be ascribed to the examination but was a result of a progression of the advanced symptoms of the inoperable lesion.

In dealing with intracranial expanding lesions, everybody will agree that it is of the greatest importance for the surgeon to have as complete information as possible concerning the nature and the extent of the lesion. Cerebral pneumography and angiography are methods which in this respect are generally the most reliable. Sometimes angiography alone gives all the information wanted, sometimes pneumography. Not seldom both methods have to be tried before all the required information is obtained. The method first used depends of course on the clinical signs and symptoms. The general indications for pneumography stated earlier in this paper obey no definite rules, but are sometimes modified according to the state and condition of the patient. For example, in some cases of suspected angioreticuloma of the cerebellum the first examination has been vertebral angiography.

There is no doubt that encephalography is a more complete examination than ventriculography and from a technical point of view a smaller procedure. We know that ventriculography is not a harmless procedure and when there is a displacement of the ventricular system the puncture of the ventricles may be difficult and cause severe damage to the brain. That is why in this series of cases encephalography was tried as a first procedure in practically every case where an air study had been considered to be indicated.

In our opinion a grouping of the tumours is necessary to allow more reliable conclusions to be drawn. Some of our groups are too small, and it is possible that in a bigger series the grouping might be more precise regarding the localization and nature of the tumour. However, we feel that from this series the following statements can be made:—

1. With the technique used and the precautions taken, the risks of encephalography in cases of brain tumour with increased intracranial pressure can practically be eliminated.

2. Of 205 cases of supratentorial brain tumour (suprasellar excluded), 101 presented with choked discs. Ventriculography had to be done in only 15 of these cases. Encephalography and angiography localized the tumour in the remaining cases.

3. Of the 36 cerebellar tumours, 30 presented with choked discs. In 23 of these cases ventriculography had to be done; encephalography localized the tumour exactly in three. In another five cases the appearance of the cisterns localized the tumour in the correct hemisphere.

4. A study of the cisterns is of great value in differentiating between extra- and intra-pontine lesions and for the demonstration of pontine angle tumours too small to cause displacement of the ventricular system.

5. The answer to the question in the title of the paper should in our opinion be, with the technique used, encephalography can and should be performed in practically every case where an air study is indicated. Even in those cases where ventriculography is necessary for examination of the ventricular system, encephalography is often of great value and should be performed as a first procedure.

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ISCHAEMIC AND POST-ISCHAEMIC NUMBNESS AND PARAESTHESIAE

BY

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During the last 10 years much interest has been taken in the sensory and motor phenomena associated with the occlusion of the blood supply to a nerve. As only a sphygmomanometer is needed to carry out the experiment, it seems desirable for all physicians to become acquainted with the disturbances of sensation that ensue, for the experiment reproduces in a short time many of the subjective sensory disturbances for which patients seek medical advice. When this simple method of investigation is carried out on patients, it may bring out abnormalities in function that are too slight to be detected by other clinical methods. The results of investigating certain clinical conditions by occluding and releasing the blood supply to the limbs have been published recently. Gilliatt and Grahame Wilson (1953) used this procedure to establish the diagnosis of the carpal-tunnel syndrome, and later Gilliatt (1955) showed that in patients with spinal cord lesions the time to numbness following occlusion of the circulation provides a good indication of the progress of the condition. Poole (1956a) established the limits of the normal by recording the duration and severity of ischaemic and post-ischaemic paraesthesiae in 93 normal subjects; and he later reported the changes found in these paraesthesiae in polyneuritis (1956b) and in motor neurone disease (1957).

As a result of the work of Lewis, Pickering, and Rothschild (1931), Lehmann (1937), Kugelberg (1944, 1948), Sinclair (1948), Merrington and Nathan (1949), Kugelberg and Cobb (1951), Marshall (1952, 1953), and Cobb and Marshall (1954), it is now known that the following events occur when the blood supply to a nerve or to a certain adequate length of nerve is occluded.

A few minutes after the occlusion has started, the nerve fibres of the *A* group become hyperexcitable. This increased excitability is sufficient to result in the fibres firing off spontaneously. When this spontaneous firing occurs in certain sensory fibres of the *A* group, tingling in the cutaneous distribution of the nerve is felt. As the period of occlusion of the circulation is continued, the nerve fibres pass through a stage of normal excitability, and eventually after a stage of decreased excitability reach a stage of complete inexcitability. When this stage is reached, the digits feel numb or " dead "; at the same time the small muscles of the hand or foot become paralysed. In the upper limb this occurs about 25 minutes and in the lower limb about 30 minutes after the onset of the occlusion. On restoration of the blood flow, the nerve rapidly regains its ability to conduct. The fibres of the *A* group first pass through a stage of increased excitability, longer lasting and far more intense than that occurring during the ischaemic period. At this stage the long motor and sensory fibres of the *A* group fire off spontaneously. This is manifested with regard to the motor fibres by fasciculation in the muscles supplied by the nerve and even by tetanus; with regard to the sensory fibres spontaneous firing is manifested as paraesthesiae. If at this stage the nerve is stimulated electrically, single impulses are transformed into double or multiple impulses. The work of Bazett and McGlone (1929, 1932) and of Merrington and Nathan (1949) shows that the various forms of paraesthesiae are related to the groups of fibres subserving various sensations, namely, the thermal paraesthesiae from discharges of the fibres subserving thermal sensation, tingling from discharges of the fibres subserving touch, pricking from discharges of the fibres subserving pressure in the skin, and pseudo cramp from discharges of the afferent fibres from muscle. Ten to 15 minutes after an occlusion lasting 20 minutes the excitability of the fibres returns to normal; at this time the subject no longer experiences any abnormalities in motor or sensory function. These changes in excitability are more prominent in the large peripheral nerves (median, ulnar, sciatic) than in small nerves. And it seems to be that the increased excitability is more marked in the proximal than in the distal parts of the nerves. It is known that all the changes mentioned occur in the nerves and not in the end-organs.

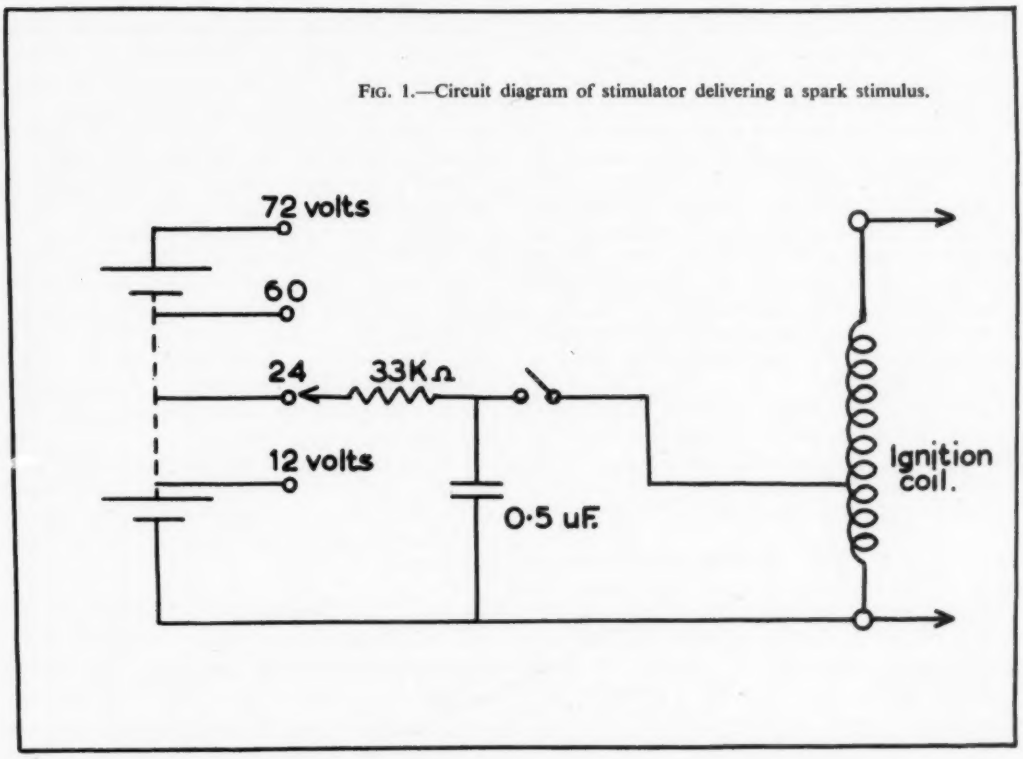


FIG. 1.—Circuit diagram of stimulator delivering a spark stimulus.

The tingling felt during ischaemia is called "ischaemic tingling" and the paraesthesiae after restoration of the blood supply "post-ischaemic paraesthesiae".

At the times when paraesthesiae occur, interference with the perception of exteroceptive stimuli has been noted. Kugelberg (1944) noticed that when ischaemic tingling is pronounced "the appreciation of touch with a piece of cotton-wool is evidently diminished." Gilliatt and Grahame Wilson (1954) found that during the periods of ischaemic and post-ischaemic paraesthesiae tactile stimuli applied to the area supplied by the spontaneously discharging nerves are not felt or the response is diminished. A failure to appreciate cutaneous stimuli occurs at the times when the nerve is in a state of increased excitability. It is apparent that an investigation of this phenomenon may throw light on the mechanism of disorders of sensation experienced by patients suffering from a variety of disorders. The purpose of this paper is to report the results of an investigation on the numbness that occurs when nerve fibres are in a state of increased excitability.

Methods of Investigation

Stimuli of various kinds were applied at intervals of one minute to the dorsal surface of the ultimate phalanx of the big toe, index, or little finger immediately proximal to the nail.

The following methods of stimulation were used:—

(1) von Frey hairs for tactile stimulation which were made of nylon suture thread, and calibrated by being weighed against a balance. The weight in grams at which the hair started to bend was divided by the radius of the hair in millimetres, this figure denoting the "strength" of the hair; (2) the *Weber'sche Tastzirkel* (usually called in English, a two-point discriminator).

For pain sensibility (3) weighted needles, and (4) a modified version of the instrument designed by Bishop (1943) was made by Mr. H. B. Morton; the circuit diagram is shown in Fig. 1. The stimulus applied by this instrument consists of a spark, the spark gap being about 1 mm. The primary winding of the ignition coil was fed with a charge accumulated in a 0·5 microfarad capacitor charged from the selected input voltage through a 33 kilo-ohm resistor. The switch was in the primary circuit. The voltage used was 60 or 72 volts. The spark which this instrument gives was applied as follows. A screw connected to the output was sunk in a perspex block, which fitted the terminal phalanx; it was fixed on the digit by rubber bands. By raising or lowering the screw, the size of the spark gap could be varied. The advantage of such a stimulator, as Bishop (1944) maintained, is that the electrical stimulus is sharply localized and of shorter duration than any mechanical stimulus; moreover, it causes no deformation of the skin. Applied to the skin of the terminal phalanges, just proximal to the nail, this spark usually gives rise to a sensation of pricking pain. If, instead of this prick, either a slight tap or a pain so slight that it was hardly painful was experienced, then the perspex application was moved a millimetre or so,

until a place was found where stimulation gave a sharp, painful prick; this sensation was immediate and not delayed. It was possible to show that the impulses set up by this form of stimulation were not transmitted in *C* fibres. On theoretical grounds alone, the rising time of the spark stimulus is so short that it would be unlikely to give rise to impulses in fibres having such good accommodation as *C* fibres. It was readily shown, by occluding the circulation to the limb, that the spark stimulus no longer aroused a sensation when only *C* fibres remain conducting; indeed this stimulus ceased to arouse a sensation before the von Frey hair ceased to do so. Thus it may be concluded that this instrument causes impulses in fibres normally used for the sensation of pricking pain, but not the *C* fibres.

(5) The electrical stimulation devised by Dawson and reported by Dawson and Scott (1949) and Dawson (1956) was applied through ring electrodes around the fourth and fifth digits of the upper limb; it caused a sensation best described as a slightly painful, heavy blow on the digits.

The stimuli, apart from that using the ring electrodes, were applied in the following manner: The point less than 1 mm. diameter at which the stimulus was applied was marked in ink. The number of affirmative answers to 10 stimulations was noted at each minute. On most occasions all 10 stimuli were applied within the first 30 seconds of the minute. Before each group of 10 stimuli, the subject was warned by the words " Ready ? Now ! " The rate of application of the stimuli was random, a rhythm of stimulation being studiously avoided. It was found that provided the stimuli were not applied too rapidly, hallucinations of touch were very rare in most subjects; they did occur, however, when sensibility began to fail completely, after about 20 minutes of occlusion in the upper limb; each hallucination was then scored as a missed real stimulation. The von Frey hairs were applied in such a manner that the distance between the tip of the hair and the skin was about 1 cm. before the hair was lowered on to the skin; the hair was pressed on to the skin until the hair bent, and care was taken to apply the hair on each occasion in as similar a manner as possible.

The two-point discriminator was used with a distance of 2·5 cm. between the points; the results were scored, in order to permit the graphic presentation, as follows: *A* = correct response with no difficulty in judging; *B* = doubtful response, with difficulty in judging; *C* = wrong response or complete inability to judge.

Vascular occlusion was obtained by using the ordinary sphygmomanometer cuff on the arm and a specially designed wide cuff on the thigh. A standard position on each limb was used: the cuff was placed on the thigh with its lower edge 4 to 5 cm. above the upper edge of the patella, and on the arm with its lower edge 1 to 2 cm. above the medial epicondyle.

The skin of the limb was kept at a nearly constant temperature by placing the limb within the field of radiation of heating lamps arranged in an inverted cradle. The skin temperature was monitored by means of a thermojunction.

Electrical stimulation was used by means of the ring electrodes. Records of the nerve action potentials through the skin were, with minor modifications, made in the way described by Dawson and Scott (1949) and Dawson (1956). The compound action potential due to the ascending volley was recorded at two places over the ulnar nerve by two pairs of electrodes: one pair was placed distal to the sphygmomanometer cuff, just above the wrist, and the other pair proximal to the cuff, just above the elbow. An earth connexion was made to a place on the flexor surface of the forearm. In order to obtain adequate relaxation so as to avoid obscuring the induced action potential by artifacts due to muscle action potentials, the subject lay on his back with his upper limb supported on straps slung from a beam. The stimulus on the digits applied by the ring electrodes gave rise to a single synchronous impulse, which, it is known, is conducted in large fibres.

The experiments carried out on healthy subjects are not all given in the paper; a typical one is chosen from a series of similar experiments performed on at least 10 healthy subjects. Experiment 8 is one of three similar experiments.

Experimental Findings

The phenomenon under investigation is best shown by Experiment 1, illustrated diagrammatically in Fig. 2.

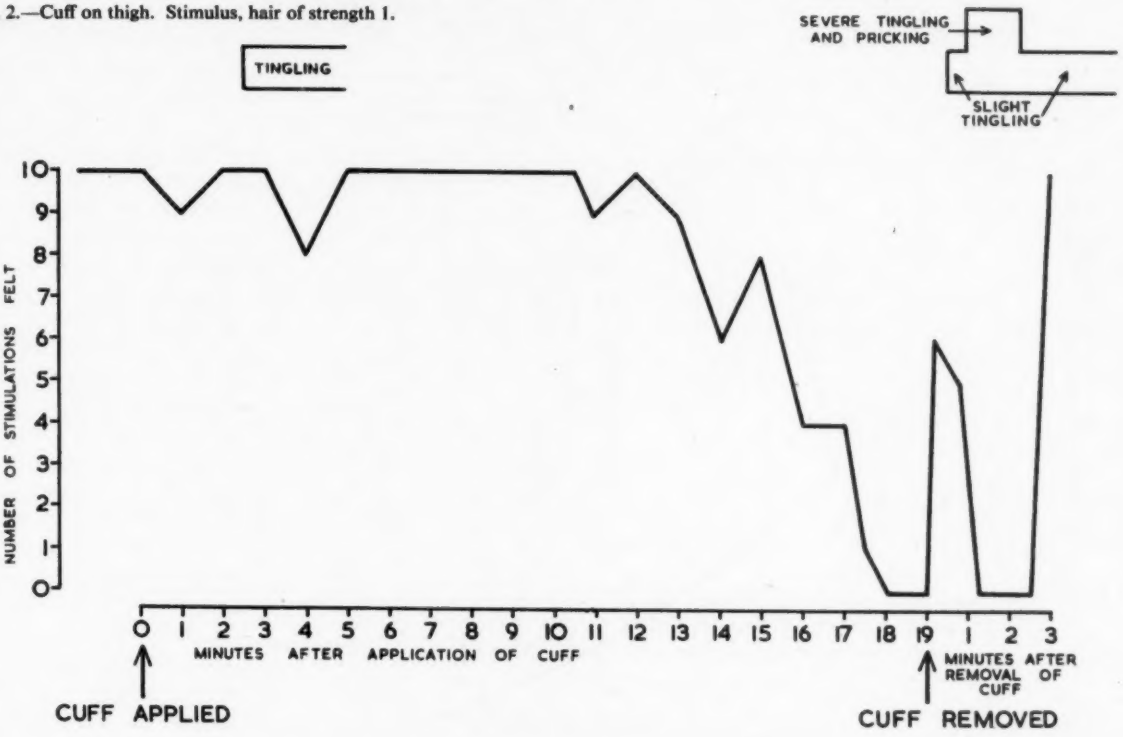
Experiment 1 (Fig. 2).—The stimulus was a von Frey nylon hair No. 3, strength 1. Before the cuff was placed on the thigh, the subject, a healthy male aged 32, was stimulated 50 times on the dorsum of the big toe, to be certain that the hair strength was above threshold. The period of occlusion was 19 minutes.

As can be seen from Fig. 2, during the phase of ischaemic tingling, the ability to feel the stimulation was very slightly impaired. During the phase of post-ischaemic paraesthesiae, the temporal pattern of disturbance of the ability to feel the stimulus of the hair was found. Within half a minute of releasing the cuff, the stimuli were felt again; in this experiment 7/10 were felt. Three-quarters of a minute after releasing the cuff, post-ischaemic tingling and pricking started, at which time some of the stimulations were still causing a sensation. By the time the post-ischaemic paraesthesiae were fully developed no stimuli with the hair could be felt. Three minutes after releasing the cuff, the appreciation of the stimuli was fully restored; the post-ischaemic paraesthesiae were by this time diminishing, though some tingling remained.

The temporary slight hypoaesthesia accompanying the ischaemic tingling is not easily observed. If the stimulus is too strong, no diminution in the number of correct responses is found; the stimulus strength has to be just threshold in the normal period. The failure to respond to the stimuli is not due to boredom or to lack of attention. If the experiment is carried out again, omitting the application of the cuff, the subject continues to respond to all the stimuli applied throughout every minute of the 22 occupied by the test.

The failure to respond to the stimulation is more

FIG. 2.—Cuff on thigh. Stimulus, hair of strength 1.


SEVERE TINGLING AND PRICKING
SLIGHT TINGLING
TINGLING
NUMBER OF STIMULATIONS FELT
0 1 2 3 4 5 6 7 8 9 10
0 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 1 2 3
MINUTES AFTER APPLICATION OF CUFF
MINUTES AFTER REMOVAL OF CUFF
CUFF APPLIED
CUFF REMOVED

definite during the period of post-ischaemic paraesthesiae; then, even the application of relatively heavy hairs evoked no response.

Although this failure to feel exteroceptive stimulation is only slight in the ischaemic phase among healthy people, in patients with pathological conditions of the nervous system this failure is more pronounced. Experiments on patients with very slight defects of sensibility show the inability to feel the stimulation in a marked form. An example is presented in the next experiment.

Experiment 2 (Fig. 3).—A similar experiment to Experiment 1 was carried out on a patient suffering from meningo-vascular syphilis. In this patient the threshold for touch sensibility was very slightly raised. A stimulus of a nylon No. 1 hair, weight 0·05 g., was applied to the dorsum of the little finger just proximal to the nail; the cuff was in the standard position. A diminution in the number of correct responses occurred at the first minute and continued till the end of the sixth; this was concurrent with ischaemic tingling. The diminution in the response to stimulation was more intense than is found in healthy subjects.

How the diminution in sensation is related to the strength of the stimulus is shown in the next experiment, carried out on a healthy subject.

Experiment 3 (Fig. 4).—Two strengths of stimulus were

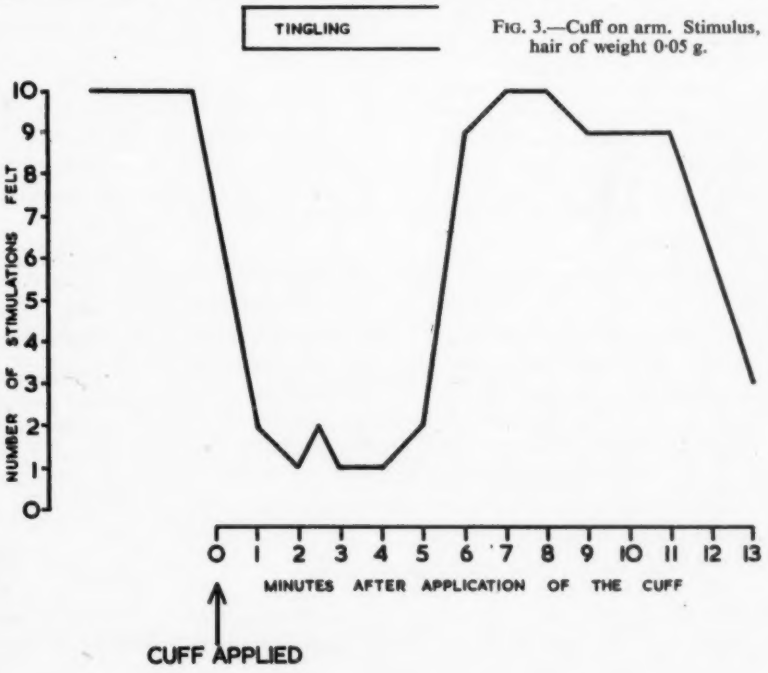

TINGLING
NUMBER OF STIMULATIONS FELT
0 1 2 3 4 5 6 7 8 9 10
0 1 2 3 4 5 6 7 8 9 10 11 12 13
MINUTES AFTER APPLICATION OF THE CUFF
CUFF APPLIED

FIG. 3.—Cuff on arm. Stimulus, hair of weight 0·05 g.

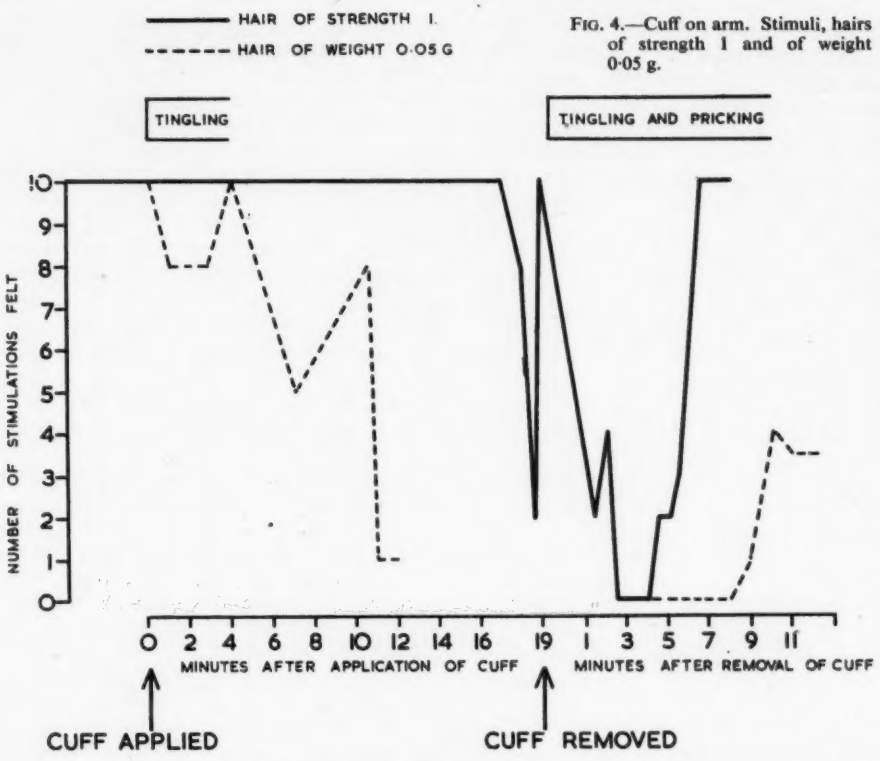

HAIR OF STRENGTH 1
HAIR OF WEIGHT 0·05 G
TINGLING
TINGLING AND PRICKING
NUMBER OF STIMULATIONS FELT
0 1 2 3 4 5 6 7 8 9 10
0 2 4 6 8 10 12 14 16 19 1 3 5 7 9 11
MINUTES AFTER APPLICATION OF CUFF
MINUTES AFTER REMOVAL OF CUFF
CUFF APPLIED
CUFF REMOVED

FIG. 4.—Cuff on arm. Stimuli, hairs of strength 1 and of weight 0·05 g.

applied to the left index of a healthy male aged 32: the stimuli were nylon No. 1 and No. 3 hairs. With the nylon No. 3 hair, stimulation readily causes a sensation recognized as an easily felt touch; with the nylon No. 1 hair, the sensation is slight and needs the full attention of the subject for its appreciation. Stimulation was just proximal to the nail. Before the period of occlusion, which lasted 19 minutes, the heavier hair was felt 50 out of 50 times and the lighter hair 46 out of 50 times.

From Fig. 4 it can be seen that during the time of ischaemic tingling the heavier stimulus continued to be felt but the lighter was not felt on all occasions. During the period of maximal post-ischaemic paraesthesiae, there was a period during which neither stimulus was felt; the appreciation of the heavier stimulus returned before that of the lighter.

Three points are brought out by this experiment: (1) only a very light touch stimulus is blocked during the ischaemic tingling; (2) in the post-ischaemic phase the light touch stimulus may not be felt immediately after restoration of the circulation; a heavy stimulus may be felt fully and normally within 1·5 minutes of restoration of the circulation; it is no longer felt, however, when paraesthesiae are at their height; (3) in the post-ischaemic period even slight paraesthesiae prevent the lightest stimuli being felt.

The disturbance of sensibility is confined to the cutaneous distribution of the nerves involved by the ischaemia. If, instead of a cuff occluding the circulation to the whole limb, a clamp is applied to a single nerve so as to obstruct its blood supply over a distance of 5 cm. or more, then all the phenomena will be restricted to the distribution of that nerve. If the ulnar nerve is compressed, then ischaemic and post-ischaemic paraesthesiae will be felt only within the cutaneous distribution of that nerve. The touch stimuli applied to the two sides of the fourth digit, one being within the ulnar and the other within the median territory, give rise to different experiences during the periods of paraesthesiae; all those applied to that half of the digit supplied by the median nerve continue to be felt, whereas a percentage of those applied to the other half of the digit are missed. Though the two points stimulated be only ½ cm. apart, the subject is able to appreciate very light touches on the median half of the fourth digit while he experiences showers of paraesthesiae on the ulnar half of the digit.

The next problem was to find out if this obliteration of sensation is limited to that provoked by very slight stimulation with nylon hairs. It was found that the alteration of sensation is not merely limited to touch caused by the von Frey hairs. For, during the post-ischaemic phase, the sensation induced by rubbing the fingers together feels altered, blurred, or, in the words of most patients, it feels " numb ". The following experiment also shows that there is a disturbance of those forms of sensibility needed in discriminating two points.

Experiment 4 (Fig. 5).—The cuff occluding the circulation was placed on the thigh of a healthy male aged 30. Two forms of stimuli were applied to the dorsum of the second digit, namely, a nylon No. 3 hair and the two-point discriminator with the points 2·5 cm. apart. It was found that during the ischaemic tingling the subject was unable to feel all the stimuli with the von Frey hair and was unable also to discriminate the two points with certainty.

It may thus be concluded that heavier touch sensibility is also obliterated during the time of the

paraesthesiae. This was also shown on innumerable occasions when heavier von Frey hairs were used. Although the subjects continued to feel all such stimuli, they noticed that the sensation aroused was less distinct during the times of paraesthesiae.

It was decided next to find out if during the periods of paraesthesiae there is alteration in the threshold for painful stimuli.

Experiment 5 (Fig. 6).—The stimulus was the "sparker" mentioned under "Methods". The voltage was 60; the perspex applicator was fixed on the tip of the big toe of a healthy male aged 40. The pressure in the cuff was kept raised for 13 minutes. The number of stimuli felt is plotted in Fig. 6. However, in experiments where a painful stimulus is used, it is more important to record the sensations of the subject. The subject reported as follows:

At 3 min., "The stimulus feels about half as strong as previously."

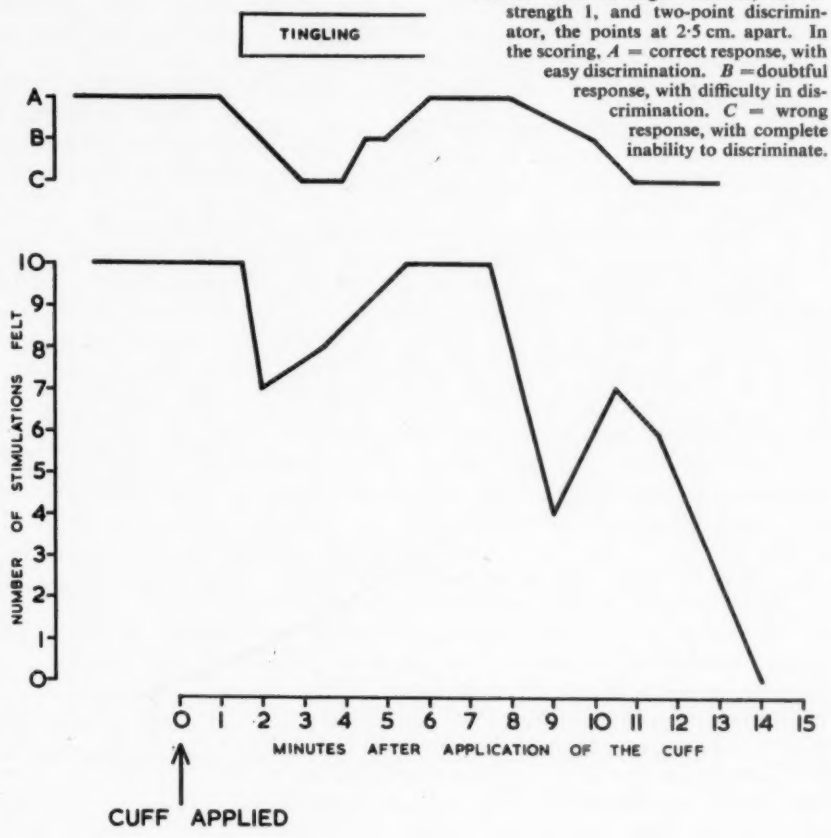

TINGLING
A
B
C
NUMBER OF STIMULATIONS FELT
0 1 2 3 4 5 6 7 8 9 10
0 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15
MINUTES AFTER APPLICATION OF THE CUFF
CUFF APPLIED

FIG. 5.—Cuff on thigh. Stimuli, hair of strength 1, and two-point discriminator, the points at 2·5 cm. apart. In the scoring, *A* = correct response, with easy discrimination. *B* = doubtful response, with difficulty in discrimination. *C* = wrong response, with complete inability to discriminate.

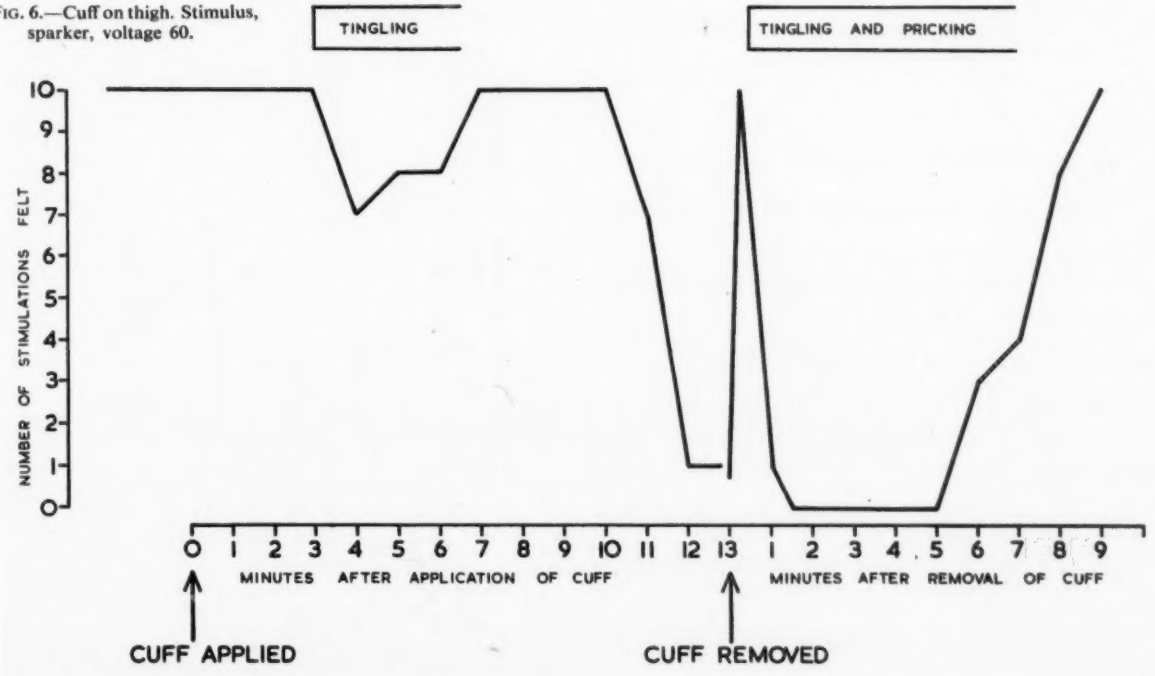

TINGLING
TINGLING AND PRICKING
NUMBER OF STIMULATIONS FELT
0 1 2 3 4 5 6 7 8 9 10
0 1 2 3 4 5 6 7 8 9 10 11 12 13
MINUTES AFTER APPLICATION OF CUFF
1 2 3 4 5 6 7 8 9
MINUTES AFTER REMOVAL OF CUFF
CUFF APPLIED
CUFF REMOVED

FIG. 6.—Cuff on thigh. Stimulus, sparker, voltage 60.

At 5 min., " It is still very weak." The two stimulations that were not felt caused no sensation of any kind.

At 6 min., " They are quite unlike the original pricks."

At 7 min., " Now they feel the same as they did originally."

At 8 min., " They are exactly the same as they were originally."

At 9 min., " The stimuli are slightly weaker, but they are still painful pricks."

At 10 min., " Very weak, but still painful pricks."

At 11 min., three stimuli caused no sensation.

During the post-ischaemic phase, all the stimuli were felt half a minute after release of the cuff; of these, the first five seemed to the subject to be about half the full strength, the second five of full strength. Then, until five minutes after release of the cuff, no stimuli were felt; nine minutes after release, although the stimuli were felt, the sensation aroused was still about half normal.

It will be seen that the plotted curve closely resembles the curves obtained when a light touch stimulus is used. A difference is that the inability to feel the painful stimulus during the post-ischaemic phase lasted a long time, as did the paraesthesiae.

It is not always possible to discriminate objectively an alteration in sensation when subjectively the alteration may be marked; this is especially likely when the sensation is that of pricking pain. Although, in the next experiment, 10 out of 10 stimuli from the " sparker " continued to be felt as pricking pain throughout the period of ischaemia, the quality of the sensation changed. This change in quality occurred at a time when in some subjects a quantitative change was demonstrable.

Experiment 6.—The input voltage of the " sparker " was 72. The cuff was placed on the thigh of a healthy male aged 32. The stimuli were applied to the dorsum of the second digit. The subject reported as follows:

At 3 min., " Some of the sting has gone out of the pricks."

At 4 min., " It feels the same; some of the sting has gone."

At 5 min., " Not all the stimuli have the same intensity."

At 6 min., " They feel definitely duller."

At 7 min., " Now they all feel sharper. They feel about the same as they did before the cuff was put on."

At 8 min., " Very slightly duller; but not as dull as they were earlier on, at about three minutes."

At 10 min., " Duller, less sharp in quality."

At 11 min., " Toes are slightly numb when rubbed."

At 12 min., " This numbness is definite. Now some of the spark stimuli are quite definitely not pricking at all; they have become touches."

Half a minute after release of cuff, nine stimuli were felt as touch, one as prick.

One and a half minutes after release, the paraesthesiae are marked. " I cannot really tell if the stimuli are like pricks or touches."

At 2 min. after release, two stimuli felt as touch, eight not felt at all.

At 3 min. after release, two stimuli felt as very slight pricks, eight felt as touch.

At 5 min. after release, all 10 felt as the same pricking sensation as at the beginning of the experiment.

This experiment illustrates the fact that, when all the stimulations arouse a sensation, during the periods of paraesthesiae the quality and intensity particularly of the sensation is altered.

Also within the modality of pain, the heavier of two stimuli may be felt at the time of the paraesthesiae, while the lighter is not. This is illustrated in the following experiment.

Experiment 7 (Fig. 7).—The stimuli were pins weighted with 5 and 20 g. The cuff was on the thigh of a healthy male, aged 36, for 22 minutes. The results for the period after release of the cuff are shown in Fig. 7. There is the usual obliteration of sensation during the period of intense paraesthesiae; the responses to stimulation with the 5 g. pin are lost far longer than those with the 20 g. pin.

All the experiments reported so far have been repeated, using a clamp to occlude the circulation only to a certain length of a single nerve. All the phenomena described above occurred, though the changes were of a slighter degree. It may therefore be concluded that the alteration of the sensations of light touch, of heavy touch or skin pressure, and of pricking pain, are not the result of ischaemia

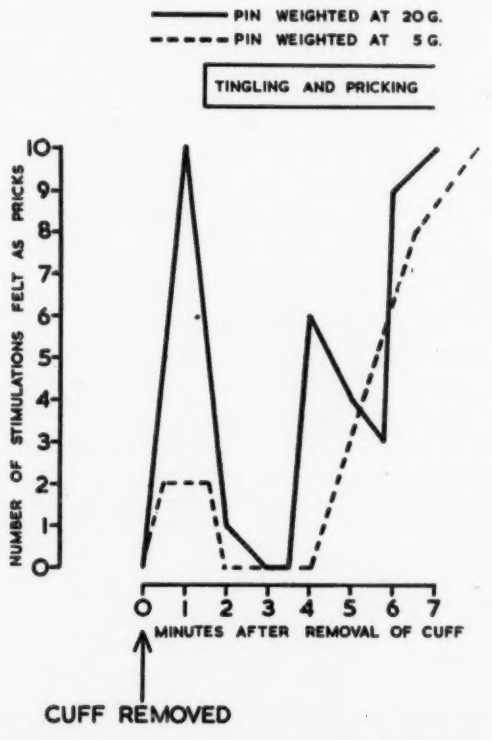


FIG. 7.—Cuff on thigh. Stimuli, pins weighted at 5 and 20 g.

of the end-organs* but of the nerve itself.

In considering the mechanism causing the raising of the threshold, it is unlikely that it is due to an inability of the nerve fibres to conduct impulses, for the period of ischaemic tingling is followed by a period of perfect conduction during which all stimuli are felt. Again, during the post-ischaemic phase, on release of the vascular occlusion, all or almost all of the stimuli are felt, showing an apparent recovery of the nerve's ability to conduct, and yet a few seconds later, when recovery would be thought to have progressed, the threshold to stimulation is raised again.

Two different explanations of this raised threshold to sensory stimulation may be considered. One explanation offered is that the impulses caused by the test stimulus cause insignificant effects within the central nervous system already bombarded by a profusion of impulses arriving from the nerve which is discharging spontaneously. This overwhelming of the signal could be occurring at some level in the central nervous system, yet it need not be conceived as necessarily involving consciousness. Another explanation offered is that the impulses caused by the test stimulus travelling orthodromically are blocked by antidromic impulses arising spontaneously within the nerve fibres in the region of ischaemia. These two groups of impulses travelling towards each other from opposite ends of the fibre could extinguish each other. Whether the impulses due to peripheral stimulation would get through to the central nervous system or not would depend on the number generated in a unit of time and the number of spontaneous impulses generated; eventually some peripherally arising impulses would get through the region of spontaneously firing impulses, if the former are arising faster; and conversely, if they arise less frequently than those generated spontaneously in the hyperexcitable nerve fibres, then they would be obliterated before they reached the central nervous system.

*The term " end-organ " is used not to imply any histologically demonstrable structure. Physiologically there is reason to believe that the termination of a nerve (the receptive element) has special properties, different at least quantitatively from those of the nerve itself (the conducting element). The term is used here to mean this physiological aspect of the receptive element.

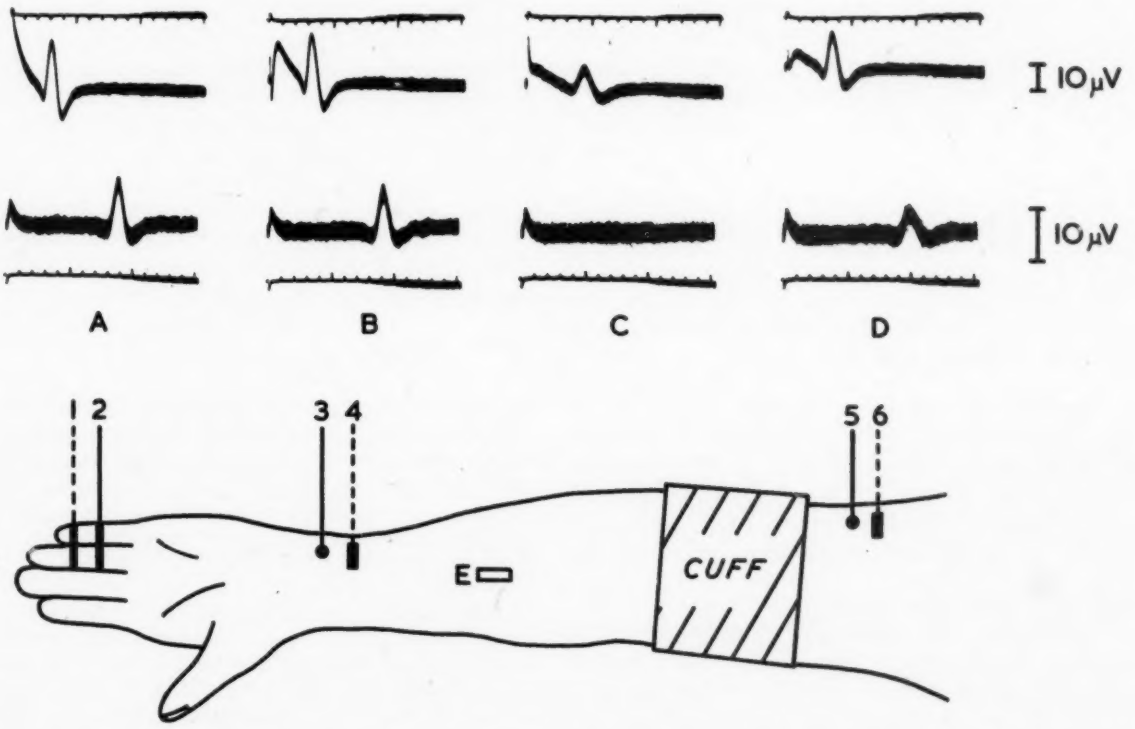
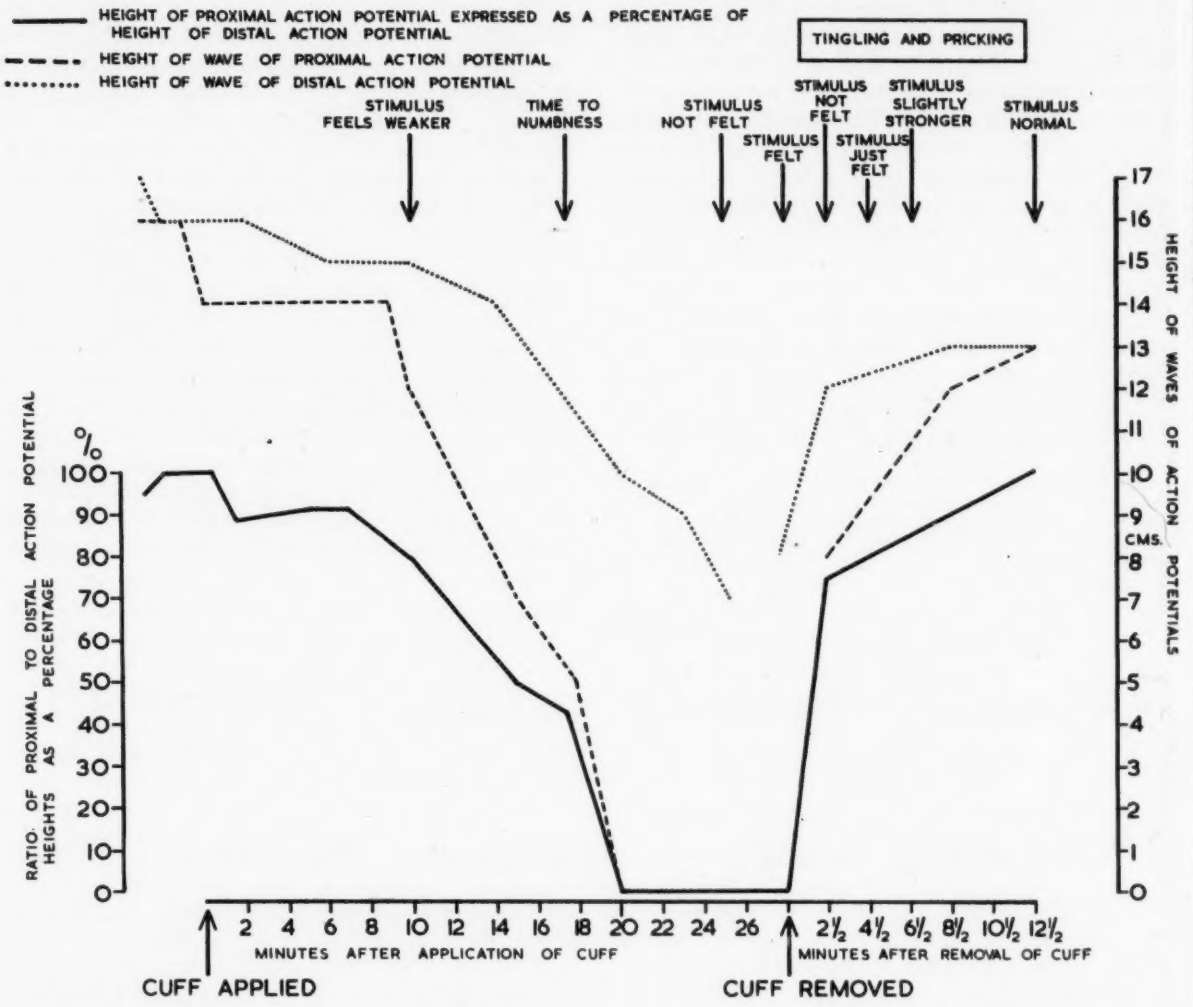


FIG. 8a.—Superimposed tracings of the action potentials produced by stimulating the fourth and fifth digits recorded over the ulnar nerve at two places. The upper tracing shows the centripetal volley recorded at electrodes 3 and 4, and the lower tracing the volley recorded at electrodes 5 and 6. The time scales show 1 and 5 milliseconds. In the diagram of the upper limb, electrodes 1 and 2 are ring electrodes used for stimulation, 3 and 4 are the electrodes over the ulnar nerve distal to the cuff, and 5 and 6 are the electrodes over the ulnar nerve proximal to the cuff. An earth connexion was made at the plate placed on the forearm at *E*. Records *A*, *B*, *C*, and *D* were taken respectively before the cuff was applied, five minutes and 25 minutes after the cuff was applied, and 2·5 minutes after release of the cuff.

FIG. 8b.—The heights of the waves of the action potentials distal and proximal to the cuff are plotted, and also the ratio of the proximal to the distal height, expressed as a percentage.



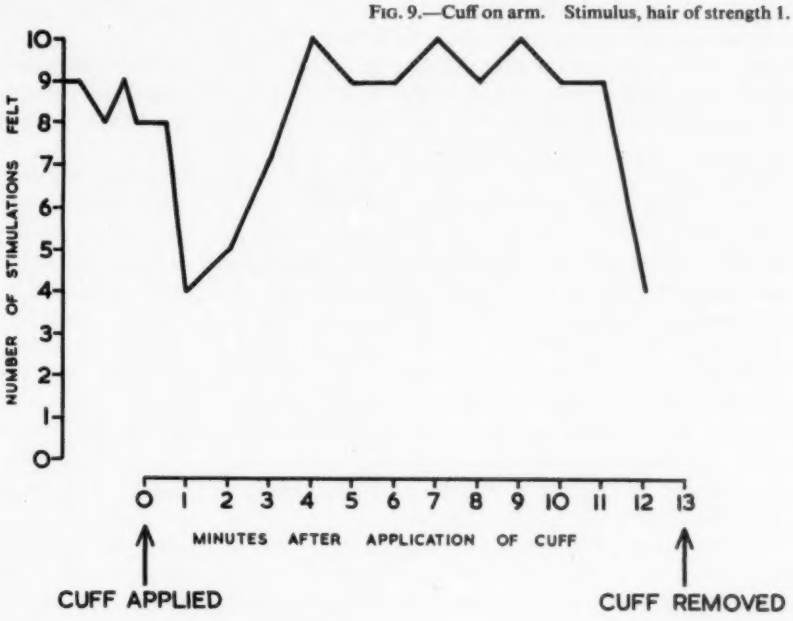
Thus, the question to be decided is whether the normal pattern of impulses needed for sensation fails to arrive at the central nervous system owing to being blocked in the peripheral nerve, or whether this normal pattern does arrive and is disturbed within the central nervous system owing to the concomitant arrival of impulses spontaneously generated in the same nerve.

Experiments were performed to find out if the impulses derived from electrical stimulation were arriving at the central nervous system and yet were not giving rise to sensation at a time when paraesthesiae were being experienced. The following experiment was carried out with the help of Dr. G. D. Dawson and Dr. R. W. Gilliatt, the latter on this occasion being the subject.

Experiment 8 (Figs. 8a and 8b).—The arrangement of electrodes has been described in the section on "Methods"; it is illustrated in Fig. 8a. The action potentials produced by stimulating the fourth and fifth digits were recorded distal and proximal to the cuff, placed over the elbow. In Fig. 8b are plotted the heights of the proximal and distal action potentials, expressed as a percentage. During the early post-ischaemic period, at 2·5 minutes after release of the circulation to the limb, the subject was unable to feel the stimulus; in fact, in this actual experiment, he asked Dr. Dawson to look at the stimulating electrodes, as he felt sure that they must have slipped off. At this time it can be seen from Fig. 8a (*D*) that there was a large action potential proximal to the cuff. It may then be concluded that the impulses were passing into the central nervous system. This inability to feel the stimulus occurred at a time when the size of the compound action potential proximal to the cuff was 75% of that distal to the cuff. During the ischaemic phase, when the compound action potential proximal to the cuff was

75% to 80% of that distal to the cuff, the stimulus had been clearly felt; and it had been felt even when the proximal action potential was too small to be recorded. Further, within the first half-minute of restoration of the circulation, before the paraesthesiae had begun, the stimulus was felt; and at this stage the size of the action potential both distal and proximal to the cuff was less than what it was later, when the stimulus causing this action potential failed to give rise to any sensation.

FIG. 9.—Cuff on arm. Stimulus, hair of strength 1.



This and other similar experiments show that when paraesthesiae are severe, strong stimulation within the cutaneous distribution of a nerve does not arouse a conscious sensation, although the volley due to this stimulation can be shown to pass along the nerve towards the central nervous system. Thus, of the two hypotheses proposed, the evidence suggests that the one is true which states that there is a disturbance in the central nervous system which gives rise to the failure to feel the test stimulus. Experiments such as Experiment 8 also show that, during the periods of spontaneous generation of impulses, the whole nerve is capable of conducting single synchronous volleys. While this holds true for electrical stimulation, it would appear to be justified to suppose that the same applies to the impulses set up by stimulation with more natural forms of stimuli, as with a hair, with the two-point discriminator, and with a needle.

That the masking of sensations arising in the periphery is caused by some central disturbance might also be deduced from two of the experiments reported above, namely, Experiments 6 and 7. In these experiments, during the post-ischaemic paraesthesiae the sensation of pain was not aroused when appropriate stimulation was applied. It is known that the nerve fibres concerned in the mediation of pain sensibility do not discharge spontaneously during the post-ischaemic period. Thus a peripheral mechanism does not account for the obliteration of sensation also in these two experiments.

The impulses arising spontaneously do not have to arouse a conscious sensation before obliteration of the sensation aroused by peripheral stimulation takes place. This is seen when an experiment is carried out on the lower limb; often in this limb no ischaemic tingling is experienced. At the time when such paraesthesiae occur in the upper limb, namely, about one to three minutes after occlusion of the circulation, there is in the lower limb the usual inability to feel light touches. Thus, this sensation is masked, even though no paraesthesiae are being felt. The same thing can occur with certain lesions affecting sensory pathways in the central nervous system. This is shown, for instance, by the following case.

Experiment 9 (Fig. 9).—Mr. W. suffered from a thrombosis of the left posterior inferior cerebellar artery. In addition to the loss of thermal and painful sensibility on the right side of the body, there was a very slight abnormality of tactile sensibility of the left upper limb. This was sufficient to prevent the sensation of ischaemic tingling, for slight lesions of the tactile pathway prevent the appearance of ischaemic tingling.

The stimulus was the nylon No. 3 hair, strength 1, applied to the left index finger, just proximal to the nail. Fifty applications were felt before the cuff was applied in the standard position. Although there was no ischaemic tingling, there was diminution in the number of responses to touch occurring at the time when ischaemic tingling is usually experienced (see Fig. 9).

In this patient interruption of the sensory pathway was within the medulla oblongata; it is probable that the lesion at this level was the cause of his failure to experience ischaemic tingling. Though in this patient the impulses usually causing tingling apparently did not enter consciousness, nevertheless, they could produce an effect which obscured the sensation due to the test stimulation. This effect presumably was not being caused below the lesion in the medulla oblongata.

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Discussion

It is usually considered that numbness results from a diminution in the number of conducting fibres. However, following the work of Gilliatt and Wilson and that reported here, it is apparent that numbness may also accompany an increased excitability of the larger nerve fibres. It may be due to such fibres spontaneously firing off impulses into the central nervous system; the reception of these impulses impairs the perception of peripheral stimulation, and this can occur even though the spontaneously arising impulses are giving rise to no sensation. Thus, numbness can be due to an inadequate number of conducting fibres; it can also be due to a large number of fibres firing off spontaneously when they are in a hyperexcitable state. No doubt this kind of numbness occurs under abnormal biochemical conditions. The changes occurring soon after the onset of vascular occlusion and very soon after the release from that occlusion are known to be the same as those produced by an increase in *p*H or a decrease in calcium ion concentration. Robinson (1955) has studied sensation in patients with tetany. He found that when a cuff is placed on the upper limbs of these patients numbness occurs twice during the period of occlusion; first it occurs at the time of ischaemic tingling, which is marked in such cases, and second when the nerve fibres cease to conduct, which they do after very short periods of occlusion of the circulation.

It has always seemed curious to me how patients tend to use the terms " numb " and " tingling " indiscriminately. That there is a reduced ability to feel peripheral stimulation during periods of paraesthesiae is now clear, and the more marked the paraesthesiae, the more definite the disturbance of peripheral sensation will be.

This is not to imply that all numbness is associated with tingling; in fact, much of the numbness of pathological conditions is similar to the velvety numbness that occurs after 20 minutes or so of an occluding cuff on the limb of normal subjects; this form of numbness is due to the failure to conduct of large numbers of the fibres.

The occurrence of these central factors in the obscuring of sensation must not lead one to account for all of the sensations associated with the periods of paraesthesiae as being due to central events. Many of these phenomena are most easily accounted for on the basis of an interaction in the peripheral nerves between orthodromic impulses and spontaneously arising antidromic and orthodromic impulses. For instance, during the period of post-ischaemic paraesthesiae, there may be a short period during which each adequate stimulation with a hair causes a feeling like a buzz continuing till the next application of the stimulus. This is most easily explained on the basis of reiterative firing and prolonged after-discharge during a phase of greatly increased excitability. When excitability is further increased, then each peripheral stimulus will cause a little volley of paraesthesiae; it is likely that the impulses due to peripheral stimulation, on reaching the region of spontaneous firing of impulses, set off groups of reiteratively firing impulses; thus they increase the spontaneous discharge. This is probably the explanation of the well-known fact that pins and needles can be increased by rubbing or pressing upon the part in which they are felt. A similar explanation probably underlies the fact that just before paraesthesiae appear spontaneously, they can be induced by rubbing or pressing the parts in which they are about to be felt.

It is surprising to find from experiments such as Experiment 8 that single synchronous volleys can get through to the central nervous system, and, under certain circumstances, give rise to no sensation. It is even more surprising to anyone who has felt the stimulus used for it is only just bearable; if it were made stronger, it would be impossible to relax the limb. If such a massive stimulus can be obliterated during the period of post-ischaemic paraesthesiae, it is likely that the same occurs for lighter and more usual kinds of stimulation.

Normal sensation depends on more complicated events than those arranged in Experiment 8. Such a single volley derived from a short stimulus, applied midway on the course of a nerve through the skin, is an artificial affair, and unlike the natural stimulation from everyday stimuli applied to end-organs. Impulses, in fact, are never single but come in battalions; trains of impulses are set off when the stimulus is applied and trains are set off when the stimulus is removed, and both are followed by an after-discharge. To alter sensation, it may be enough to alter the after-discharge or it may be enough to prolong the relatively refractory period of some fibres, so that alternate impulses, for instance, do not get through. It is unknown how much interference with the normal pattern of impulses arriving at the neurological substratum of sensation can be tolerated without there being an interference with normal sensation.

Summary

During the periods of ischaemic and post-ischaemic paraesthesiae, stimuli applied to the territory of the nerve spontaneously discharging are either not felt or they are felt in a diminished degree.

This interference with the perception of stimuli is enough to cause a real disturbance of sensation,

and it is described as " numbness " by those experiencing it.

The forms of sensibility obliterated during these periods are touch, pressure, and pain. (Thermal sensations have not been investigated.)

It was found that this " numbness " is not due to a failure of the impulses to reach the central nervous system; it is, therefore, due to some process taking place within the central nervous system.

It is concluded that numbness is not only due to a large number of fibres ceasing to conduct impulses, but it can also be due to fibres being hyperexcitable and firing off spontaneously; in such a case peripheral stimulation is not felt.

I take this opportunity of thanking Dr. George Dawson and Dr. Roger Gilliatt who performed a great many of the experiments with me and helped throughout by useful discussions, and Dr. E. Arnold Carmichael for his interest and the opportunities he provided for doing this work.

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THE SURGICAL PROGNOSTIC SIGNIFICANCE OF THE ELECTROENCEPHALOGRAPHIC PREDICTION OF AMMON'S HORN SCLEROSIS IN EPILEPTICS

BY

W. A. KENNEDY and DENIS HILL

BASED ON PATHOLOGICAL MATERIAL SUPPLIED BY

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In a previous communication (Falconer, Hill, Meyer, Mitchell, and Pond, 1955) the results of treating intractable temporal lobe epilepsy by temporal lobectomy were given. A survey was reported of the clinical, electroencephalographic, radiological, and pathological findings in 31 cases. The follow-up study of the patients showed beneficial effects upon the epilepsy and upon the personality disorder in a proportion which compared very favourably with most published series. The opinion was expressed that this was due to inclusion of the uncus, Ammon's horn, and possibly the amygdaloid nucleus in the resected tissue. Certainly it is in the anterior and medial structures of the temporal lobe that the main sites of pathological change are found (Earle, Baldwin, and Penfield, 1953; Meyer, Falconer, and Beck, 1954). Their importance in the development of temporal lobe epilepsy is also indicated by experimental work. Thus, in cats Gastaut, Vigouroux, and Naquet (1952) found that alumina cream lesions placed only in the amygdala-uncus regions could induce seizures of the temporal lobe type, and Green, Clemente, and Degroot (1957) also observed such seizures after electrolytic lesions of the medial parts of the amygdaloid complex. It was subsequently shown by both groups independently, as indicated by Green (1957), that Ammon's horn had been severely damaged in these animals. While the part played by Ammon's horn in the genesis of temporal lobe epilepsy is still not clear, in man when its sclerosis is encountered in the excised temporal lobe, diffuse and disseminated damage is also frequently present although usually associated with lesions in other medial and lateral structures. From the clinical point of view the importance of removing the deep temporal lobe structures, including the hippocampus (Ammon's horn), uncus, and amygdaloid nucleus in the operation of temporal lobectomy has also been stressed by Penfield and Jasper (1954) and recently by Rasmussen (1957).

The diagnostic and pathological data and the therapeutic effects of temporal lobectomy carried out on a larger series of 50 cases are now available and a preliminary report has been given (Falconer, Meyer, Hill, and Wilson, 1957). Following Earle *et al.* (1953) the pathological findings have been classified in two main groups. While all cases in which a space-occupying lesion could be anticipated on clinical, radiological, or electroencephalographic grounds were excluded from the series, there were, nevertheless, 14 cases in which very small focal macroscopic lesions were found in the resected tissue, 11 being either very small tumours or glial hamartomas (Group I). In the remainder (36 cases) diffuse lesions, of varying degrees of severity, were found. In the more severe, sclerosis of Ammon's horn and usually of the other medial structures was present (21 cases, Group IIa); in the less severe, sclerosis of Ammon's horn was not present (15 cases, Group IIb). In the follow-up study it was found that the most striking degrees of benefit as regards fits was seen in the tumours and glial hamartomas of Group I, since all cases were benefited, eight completely so. Of the cases with diffuse pathology (36 patients), those with Ammon's horn sclerosis were benefited to a much greater extent than those without this lesion (Table I). While the relationship between the presence of Ammon's horn sclerosis and relief from fits by surgery is suggested ($P<0.05$), that between improvement in personality with the presence of this lesion is significant at the 1% level ($P<0.01$). It therefore appears that the largest pathological subgroup, constituting over 40% of the cases with temporal lobe epilepsy submitted to surgery, are those with Ammon's horn sclerosis, and that of those with diffuse lesions, it is in this subgroup that the greatest benefit to the personality disorder and to epilepsy can be anticipated. Indeed

TABLE I

POST-OPERATIVE IMPROVEMENT IN AMMON'S HORN SCLEROSIS

Ammon's Horn Sclerosis	No.	Relief* from Epilepsy		Improvement in Personality		Improved Working Ability	
		+	−	+	−	+	−
Present.. ..	21	18	3	16†	5	16	5
Absent.. ..	15	7	8	4	11	5	10

* Relief = free of fits (12 cases) or 50% improved (6).
† Two pre-operative personalities normal.

were it possible to anticipate before operation that Ammon's horn sclerosis was present on one side, this might strengthen the decision to operate on that side in the anticipation of a good result. The contribution which electroencephalography can make towards this prediction is the subject of the present communication.

Case Material

Fifty patients submitted to unilateral temporal lobectomy by Mr. Murray Falconer at the Guy's-Maudsley Neurosurgical Unit have been followed up for periods ranging from one to five years. The pathological changes observed in the resected temporal lobes have been reported (Cavanagh, Falconer, and Meyer, 1957) and the relationships between these changes and the clinical factors assessed (Falconer *et al.*, 1957). The principles of selection of cases and the operative technique have been outlined in previous reports (Hill, 1953; Falconer, 1953; Falconer *et al.*, 1955), and the changes in learning ability and of personality studied (Meyer and Yates, 1955; Hill, Pond, Mitchell, and Falconer, 1957). The present communication reports the results of a correlation study between pathological findings and pre-operative E.E.G. data. The results indicate that on E.E.G. data alone it is possible to predict the presence of Ammon's horn sclerosis in patients suffering from temporal lobe epilepsy.

Electroencephalographic Techniques

In our previous reports the importance has been stressed of repeated E.E.G. examinations to locate the focus and to determine, in the case of bilateral foci, which is the dominant one. As Gibbs and Gibbs (1947) first showed, the discharges of temporal lobe epilepsy may not appear until the patient sleeps or is narcotized with a barbiturate. Moreover, since the location of the discharges in most cases is on the anterior-inferior surface of the temporal lobe, their identification by the routine methods of scalp electroencephalography may be impossible. In the present series of 50 cases, 212 routine E.E.G.s were carried out pre-operatively. In addition 95 records were made using sphenoidal needle electrodes, the patients being narcotized in 34 cases with intravenous thiopentone (" pentothal ") and in 53 with oral quinal barbitone sodium ("seconal"); eight cases were examined by sphenoidal electrodes without drugs. Seizures were activated in five cases with intravenous " metrazol ". There were therefore a total of 312 pre-operative E.E.G. investigations.

Sphenoidal Electroencephalography.—Jasper (1949) first mentioned the use of needle electrodes placed in the region of the greater wing of the sphenoid, but the needles were introduced by an anterior approach which can be a difficult procedure. Jones (1951) first described the introduction of such needles by a lateral approach by a method which has been standardized and extensively used in this hospital (Kerridge, 1952). The details of this technique used in 166 patients were reported by Pampiglione and Kerridge (1956). In the present series the spike discharges would have been missed in one case without needle electrodes, but more importantly, in 11 cases independent spike discharges beneath the contralateral temporal lobe would have been missed. As reported earlier (Hill, 1953), the spike discharges may be located at the anterior-inferior part of the temporal lobe (the sphenoidal electrode), at the mid-temporal convexity (the ear electrode), in the Sylvian areas, or in the posterior temporal areas ; contralateral discharges may also be present in any of these areas and the spike discharges in one area may show " spread " to other areas or to the opposite side. Discharges may be evident before the introduction of narcosis, but if not, may appear either in the early or only in the deep stages of narcosis or may only appear during recovery of consciousness. Intravenous thiopentone (" pentothal ") is therefore introduced slowly, the narcosis however, being taken to the stage beyond which the corneal reflexes are lost.

Effects of Barbiturate Narcosis on the E.E.G.—Narcosis may be necessary to demonstrate the location of the predominant spike focus and its constancy, as well as the presence of other subsidiary spike foci. Of equal importance to the present study is the fact that an intravenous barbiturate induces in the normal cortex of the majority of normal individuals fast rhythm (at 16 to 28 c./sec.) of moderate voltage, an activity which in the normal brain is symmetrical in frequency and amplitude on the two sides. This fast activity, which appears first in the prefrontal areas, is seen also in all areas of the frontal, central, and temporal cortex in the early stages of narcosis. Pampiglione (1952) was the first to demonstrate the use of this phenomenon for the localization of cerebral lesions, observing that areas of damaged brain failed to show the induced fast

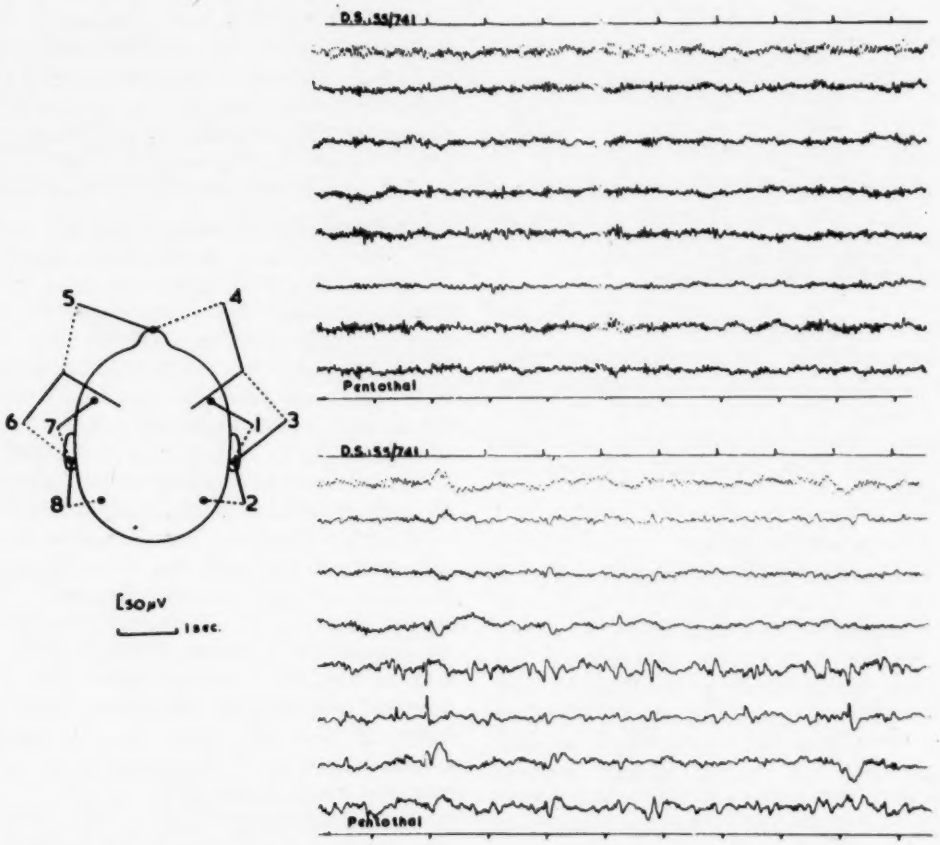

FIG. 1.—Case of left temporal lobe epilepsy with Ammon's horn sclerosis. E.E.G. record using sphenoidal needle electrodes and "pentothal" narcosis. The upper record shows the early fast rhythm stage of narcosis; the lower record is taken during recovery. The electrode schema shows that the first two channels (1 and 2) record from the scalp over the right temporal areas, and the last two channels (7 and 8) record from similar areas on the left side. Channel 3 records between the right sphenoidal electrode and the ear, and channel 6 between the left sphenoidal electrode and the ear. In the upper record channel 6 shows gross reduction of barbiturate-induced fast rhythm in comparison with channel 3. In the lower record focal spikes are seen only at the left sphenoidal electrode (channels 5 and 6). Thus the left sphenoidal area shows both a reduction of barbiturate-induced fast rhythm and focal spike discharges.

rhythm present in other areas. In the present study, data concerning the symmetry of barbiturate-induced fast rhythm in the temporal areas, as well as in convexity areas, were available in 38 cases. For this purpose the symmetry of rhythm on the two sides was compared from pairs of electrodes, placed on measured positions on the head in homologous situations. In addition comparisons were made of activity recorded between the sphenoidal needles and the nose electrode and, more significantly, between the sphenoidal needles and the ear electrodes (sphenoidal-ear electrodes) on the two sides. The latter observations have proved to be the most significant for the location of temporal lobe pathology (Fig. 1).

Pathological Findings

The pathological findings in the resected temporal lobes could be divided into two main groups, according to whether focal macroscopic lesions (Group I) were present or whether the lesions were diffuse (Group II). There were 14 cases in Group I, 36 in Group II. The latter were again subdivided into those in which there was Ammon's horn sclerosis (21 cases, Group IIa), and those in which there was no such lesion (15 cases, Group IIb). Detailed histological analysis of all elements available for study in the specimens was made, including assessments as to the extent of involvement of the medial structures (Ammon's horn, uncus, and amygdaloid nucleus), and the cortex and white matter of the lateral, inferior, and fusiform gyri. These findings have been reported (Cavanagh *et al.*, 1957). Sclerosis of Ammon's horn (Group IIa) is rarely found alone, the pathological process almost invariably including the uncus, and, in over a half of the cases in which it was available, the amygdaloid

nucleus as well. In this group also, the changes in the cortex and white matter were more severe than in the Group IIb, in which the medial structures were relatively spared. It seems probable therefore that Groups IIa and IIb are not distinctive and different pathological entities, but that Group IIa, in which the medial structures are involved, are cases in which the pathological process has been more severe, affecting all elements of the temporal lobe in greater degree than in Group IIb.

Results

The purpose of this correlation study between E.E.G. characteristics and the data of histological analysis is to find factors in the E.E.G. which will allow prediction of the sites of main pathological change in the affected temporal lobe. Allowance has to be made for the fact that the required data were not available in all cases either from the E.E.G. or the histological work. Table II sets out the results on the numbers available for each item observed for the 50 cases. The main pathological groupings will be considered first.

Group I.—This group of 14 very small focal macroscopic lesions included 11 small tumours and glial hamartomas and three other lesions (two small cortical infarcts and one traumatic scar). Eight of these cases showed a unilateral spike focus and five bilateral spike foci. One case (the only one in the series) showed no spike focus, the operation being performed on other grounds (see Falconer *et al.*, 1955). Barbiturate-induced fast rhythm between the sphenoidal-ear electrodes on the side of the focus was seen to be reduced in two cases and from convexity electrodes in five cases. While there were no E.E.G. features specific to Group I cases, and no features having predictive value, it is of interest that the proportion of strictly unilateral discharges was no greater in this focal lesion group than in the groups with diffuse lesions. In four cases with small tumours spike discharges were evident in the contralateral temporal lobe.

Group IIa.—This group of 21 cases with diffuse lesions were those with marked sclerosis of Ammon's horn as well as other medial structures. In eight cases there was a unilateral spike focus and in a further three spread of the discharges to the opposite hemisphere was observed; in 10 cases the spike discharges were bilateral and fired independently. In 16 of the 17 cases in which it was observed, the barbiturate-induced fast rhythm was reduced between the sphenoidal ear electrodes on the side of

TABLE II

RESULTS OF CORRELATING E.E.G. AND HISTOLOGICAL FINDINGS IN 50 CASES

E.E.G. Characteristics	Groups			All Cases	Medial Structures Involved		Ammon's Horn		Uncus		Amygdaloid Nucleus		Ammon's Horn and Uncus		Middle and Inferior Gyri: Cortex		Middle and Inferior Gyri: White Matter		Middle and Inferior Gyri: Cortex and White Matter		Middle, Inferior, and Fusiform Gyri: Cortex		Middle, Inferior, and Fusiform Gyri: White Matter		Middle, Inferior, and Fusiform Gyri: Cortex and White Matter	
	I	II a	II b		+	−	+	−	+	−	+	−	+	−	+	−	+	−	+	−	+	−	+	−	+	−
Unilateral E.E.G. focus	7+	8	11	26	6	13	7	16	5	14	6	11	4	15	3	22	15	11	7	19	3	22	16	10	6	20
Unilateral E.E.G. focus with spread	0	3	0	3	3	0	3	0	3	0	1	2	3	0	1	2	3	0	1	2	1	2	3	0	1	2
Bilateral foci	5	10	4	19	9	3	10	6	10	3	5	5	8	5	6	11	14	3	7	10	8	11	16	3	9	10
Reduced fast rhythm between sphenoidal-ear electrodes	2	16	3	21	14	5	15	6	15	4	8	10	13	6	6	15	18	3	9	12	6	15	18	3	8	13
Symmetrical fast rhythm between sphenoidal-ear electrodes	5	1	9	15	0	9	1	10	0	9	0	7	0	9	2	11	5	9	4	10	4	10	7	8	5	10
Reduced fast rhythm between convexity electrodes	5	11	1	17	11	3	11	4	11	3	7	5	10	4	7	8	14	1	9	6	9	8	17	0	10	7
Symmetrical fast rhythm between convexity electrodes	3	7	11	21	3	12	6	12	4	11	2	12	3	12	1	19	10	11	4	17	2	18	10	11	4	17
Unilateral focus + reduced fast rhythm	1	7	3	11	4	5	6	5	5	4	3	6	4	5	2	9	8	3	4	7	2	9	8	3	4	7
Unilateral focus + symmetrical fast rhythm	2	1	7	10	0	7	1	7	0	7	0	5	0	7	1	8	3	7	3	7	1	8	4	6	2	8
Bilateral foci + reduced fast rhythm between sphenoidal-ear electrodes	1	6	0	7	7	0	6	1	7	0	4	2	6	1	3	4	7	0	4	3	3	4	7	0	3	4
Bilateral foci + symmetrical fast rhythm	2	0	2	4	0	1	0	2	0	1	0	1	0	1	1	2	2	1	1	2	2	2	3	1	3	1
Unilateral focus with spread with reduced fast rhythm	0	3	0	3	3	0	3	0	3	0	1	2	3	0	1	2	3	0	1	2	1	2	3	0	1	2

* One case with a unilateral focus has been excluded because no sphenoidal recording was done.

the focus, and at the convexity electrodes in 11 of 18 cases in which it could be observed. Seven of the eight unilateral cases, the three unilateral cases with spread of discharges to the contralateral side, and the six bilateral cases in which the data were available, showed reduction of the barbiturate-induced fast rhythm between the sphenoidal-ear electrodes on the side of the predominant focus. Thus the finding of reduction of barbiturate-induced fast rhythm beneath the anterior part of the temporal lobe together with unilateral or bilateral spike foci favours the prediction of Ammon's horn sclerosis. The evidence supporting this becomes more precise when the individual medial structures are considered separately (see below).

Group IIb.—In this group of 15 cases with diffuse lesions in which all the medial structures, and in particular the Ammon's horn were spared, 11 showed unilateral and four bilateral spike foci. In contrast to Group IIa cases, in only three of 12 cases was the barbiturate-induced fast rhythm reduced between the sphenoidal-ear electrodes, and in only one of 12 cases at electrodes on the convexity.

The difference between the group with Ammon's horn sclerosis and the group in which this structure was spared, in respect of the fast rhythm response of the temporal cortex to barbiturates, is very striking and has greater predictive value in determining the site of the main pathological changes than any characteristic or location in the temporal areas of the spike discharges themselves. In order to determine which anatomical elements, in addition to the Ammon's horn, are involved in those cases showing this E.E.G. phenomenon, detailed assessments of the degree of pathological change in the various structures were made for all pathological subgroups, *i.e.*, in 50 cases. For this purpose the degree of involvement for each individual structure was assessed on a four-point scale, namely, $++ = 3$, $+ = 2$, $\pm = 1$, $0 = 0$ (maximal involvement = 2 or more, minimal = 1 or less). This assessment was made for the medial structures (Ammon's horn, uncus, and amygdaloid nucleus) for the cortex and white matter of the middle temporal, inferior temporal, and fusiform gyri, both for cortex alone and for white matter alone. The three medial structures were also considered together (Table II).

Specific Correlations.—In estimating chi square values, in view of the small numbers, Yates's correction was used in all calculations.

(a) *Medial Structures (Ammon's Horn, Uncus, and Amygdaloid Nucleus).*—If the cases in which spread of discharges from the dominant focus to the contralateral side are included, 12 of 18 cases with maximal involvement of medial structures show bilateral spike foci, whereas only three of 16 with no or minimal involvement show bilateral spike foci. This difference is significant at the 2% level. On the other hand, all 14 cases of maximal medial structure pathology on which data were available showed reduced barbiturate-induced fast rhythm between the sphenoidal-ear electrodes, whereas of 14 cases with minimal pathology five showed reduced fast rhythm. This difference is significant beyond the 1% level ($P<0.01$). The association of reduction of fast rhythm from convexity electrodes on the scalp over the temporal areas with maximal medial structure involvement is of equal significance ($P<0.001$).

(b) *Ammon's Horn (Hippocampus).*—Considering this structure alone, the associations with bilateral spike foci and with reduction of barbiturate-induced fast rhythm between the sphenoidal-ear electrodes are evident, and the degree of significance is at the 5% level ($P < 0.05$). This is true in the case of bilateral spike foci; for the reduction of barbiturate-induced fast rhythm beneath the temporal lobe the association is clearer ($P < 0.01$), but the relationship is less clear for the fast rhythm recorded from the scalp electrodes ($P < 0.05$).

(c) *Uncus.*—Sclerosis of this structure is very clearly associated with bilateral spike foci ($P<0.01$), with reduction of barbiturate-induced fast rhythm beneath the temporal lobe on the affected side ($P < 0.01$), and to a lesser extent with reduction of this activity on the lateral convexity from scalp electrodes ($P < 0.05$).

(d) *Amygdaloid Nucleus.*—This structure was available for histological analysis in insufficient cases to enable valid conclusions to be drawn. However, the general trends of association are the same as for the uncus and Ammon's horn, with the exception of the spike foci, since in seven of 13 cases in which this nucleus was involved, the focus was unilateral.

(e) *Cortex and White Matter.*—Consideration of Table II shows that the more extensive the pathological changes the more likely that the E.E.G. will show bilateral spike discharges and the more likely that barbiturate-induced fast rhythm will be reduced either under or on the lateral surface of the damaged temporal lobe. This is more particularly true of involvement of the white matter than of involvement of the cerebral cortex. Thus of 20 cases showing bilateral spike foci, seven showed involvement of the cortex of the middle and inferior temporal gyri, while 17 showed involvement of the white matter. Of 25 cases with unilateral spike foci, three showed involvement of the cortex and 15 of the white matter of these gyri. Thus with bilateral spike foci there is a greater chance than with a unilateral focus that the cortex will be involved, and a much greater

chance that the white matter will be so. This association is not, however, statistically significant. The relationship between involvement of the white matter of the temporal lobe and reduction in barbiturate-induced fast rhythm, both beneath the lobe ($P < 0{\cdot}01$) and on its convexity ($P < 0{\cdot}02$) is, however, clearly significant, but only at the 1% level for both observations if the fusiform gyrus is included. Again, therefore, there is evidence that for both E.E.G. characteristics, bilateral spike foci and reduced barbiturate-induced fast rhythm, the greater the involvement of medial structures, either the nuclei or the gyral cortex and white matter, the greater the chances of association with these E.E.G. characteristics.

Surgical Prognostic Significance.—In a previous communication (Falconer *et al.*, 1957) evidence was presented that good therapeutic effects from temporal lobectomy were observed within that subgroup of diffuse lesions in which the Ammon's horn was involved in the pathological changes. This is shown in Table I as regards relief of fits, improvement in personality, and in working ability. These are now considered in relation to the various E.E.G. characteristics described in the pre-operative records (Table III). These show that, for the larger series of 50 cases, contrary to previous indications (Falconer *et al.*, 1955), the unilaterality or bilaterality of the spike discharges has no influence on the therapeutic results, although of course the choice of site for surgery has hitherto depended upon predominant firing. However, one significant observation can be made as regards relief from epilepsy. This is clearly related to the finding of a reduced barbiturate-induced fast rhythm beneath the affected temporal lobe, *i.e.* between the sphenoidal-ear electrodes. This association is significant at the 1% level ($P < 0{\cdot}01$). Reduction of fast rhythm at the convexity electrodes is also associated with a good therapeutic result as regards seizures but only at the 5% level of significance ($P < 0{\cdot}05$).

TABLE III
E.E.G. CHARACTERISTICS RELATED TO POST-OPERATIVE IMPROVEMENT

E.E.G. Characteristics	Improvement in Fit Frequency		Improvement in Personality		Improvement in Working Ability	
	+	−	+	−	+	−
Unilateral E.E.G. focus	18	8	14	12	16	10
Unilateral E.E.G. focus with spread	3	0	3	0	3	0
Bilateral foci	14	5	12	7	12	7
Reduced fast rhythm between sphenoidal-ear electrodes	18	3	16	5	15	6
Symmetrical fast rhythm between sphenoidal - ear electrodes	5	10	8	7	6	9
Reduced fast rhythm between convexity electrodes	16	1	14	3	14	3
Symmetrical fast rhythm between convexity electrodes	12	9	8	13	8	13
Unilateral focus + reduced fast rhythm	8	3	7	4	7	4
Unilateral focus + symmetrical fast rhythm	5	5	3	8	4	7
Bilateral foci + reduced fast rhythm between sphenoidal-ear electrodes	7	0	6	1	5	2
Bilateral foci + symmetrical fast rhythm	3	1	2	2	2	2
Unilateral focus with spread with reduced fast rhythm	3	0	3	0	3	0

Discussion

Hitherto the selection of the side for the operation of temporal lobectomy in a patient judged on other grounds to be suitable for the operation has rested largely on the sites of spike foci in the E.E.G. When E.E.G. and radiographic data have been in conflict, the decision has been made upon the former. The decision as to which temporal lobe is involved has been made upon the finding of a predominant spike focus in the E.E.G.s which have been taken upon many occasions. When a unilateral focus has been found at a sphenoidal electrode on every occasion the decision is not in doubt. More frequently, however, contralateral and less active discharges are found and the decision as to laterality has rested upon the relative frequency of the discharges on the two sides. In many cases it is clear which is the predominant side since the relative frequencies may be of the order of 100 : 1, while relative frequencies of the order of 4 : 1 have arbitrarily been taken as the dividing line. The present study indicates that another E.E.G. characteristic, reduction of barbiturate-induced fast rhythm on the inferior surface of the affected temporal lobe, has a predictive significance greater than any other E.E.G. characteristic. This finding was observed in 21 of the 50 patients in respect of the sphenoidal-ear electrodes and in 17 patients from convexity electrodes.

The present study throws further light on the significance of the contralateral and less vigorous spike focus. In five patients with small focal macroscopic lesions in the resected temporal lobe (Group I), contralateral foci were found, and in this group it is reasonably certain that no lesion existed in the contralateral hemisphere. Moreover, the presence in the E.E.G. of bilateral spike foci is found to correlate with maximal pathological involvement of the medial structures and in particular with disease of Ammon's horn and the uncus. Of those patients with diffuse lesions, this group with Ammon's horn

sclerosis show greater improvement post-operatively as regards fits and personality disorder than those in which these structures are spared. Bilateral spike foci do not therefore exclude a focal single macroscopic lesion but only indicate the probability that whatever the nature of the lesion it is likely to be sited mainly in the medial deep structures of the temporal lobe, and, further, the presence of a contralateral spike focus is not predictive of a poor prognosis for surgery. Thus while 18 of 27 patients with unilateral spike foci were improved as regards epilepsy, 14 of 19 patients with bilateral foci were so.

We can now assess the value of these observations in predicting pre-operatively in which pathological group any given patient's lesions will be found.

Group I (Focal Macroscopic Lesions).—Of these 14 patients, eight showed unilateral foci, five bilateral foci (one no spike focus); two showed reduction of barbiturate-induced fast rhythm at the sphenoidal-ear electrodes and five at the convexity electrodes. It is not therefore possible to predict this group upon the E.E.G. findings alone.

Group IIa and IIb.—Since the distinction between these two groups is the presence in Group IIa of the main pathological changes in the Ammon's horn, the presence of bilateral foci and/or reduction of barbiturate-induced rhythm beneath the temporal lobe distinguishes Group IIa from Group IIb at the 1% level of significance.

Falconer *et al.* (1957) have pointed out that there is a difference in the age of onset of the epilepsy for the different pathological groups. Thus the Group I of focal macroscopic lesions tend to start epilepsy in adult life, and there is no history of abnormal birth or infantile convulsions. By contrast the two groups of diffuse lesions (Groups IIa and IIb) have an onset of epilepsy in early life or a history of birth trauma. It is in the differentiation of these two subgroups that the present study is valuable. The importance lies in the fact that it is those in Group IIa that the greatest therapeutic benefit from temporal lobectomy can be expected (Table I).

The E.E.G. data reported here and the predictions which can be based upon the correlation study with the histological data were available through the use of the sphenoidal-needle-narcosis technique. Without this technique such predictions cannot be made, for without this type of recording the contralateral less active spike focus would have been missed in over 50% in which it was present. Moreover, the significant finding as regards reduction of barbiturate-induced fast rhythm is that which occurs between the sphenoidal-ear electrodes rather than that which is found to a lesser extent between scalp electrodes over the temporal areas. These observations appear fully to justify the use of this technique.

Summary

The pre-operative E.E.G. data and the detailed histological data on the biopsy specimens have been studied on 50 patients submitted to temporal lobectomy for the relief of temporal lobe epilepsy.

The technique of using sphenoidal needle electrodes combined with the production of barbiturate-induced narcosis provides E.E.G. data which have predictive value in determining the sites in the temporal lobe of maximal pathological changes.

The presence of a less active contralateral spike focus in the opposite temporal lobe is found to correlate with pathological changes in the uncus and Ammon's horn of the affected lobe at the 1% level of significance.

Reduction in barbiturate-induced fast rhythm recorded between the sphenoidal and ear electrodes on the affected side correlates with lesions in these medial structures and also in the white matter of the temporal lobe at the 1% level of significance.

The E.E.G. characteristics in temporal lobe epilepsy can predict the site of maximal pathological change but by themselves cannot predict the nature of that change.

The prognostic implications for temporal lobectomy of the data are discussed.

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A REPORT OF TWO CASES OF THE JUVENILE FORM OF AMAUROTIC FAMILIAL IDIOCY (CEREBROMACULAR DEGENERATION)

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The cerebral lipidoses are rare diseases, which have few certain links in common beyond the shared facts of disturbed lipid metabolism, progressive mental deterioration coming on early in life, and a heredofamilial pattern of occurrence. In Niemann-Pick's disease, Gaucher's disease, and xanthomatosis, the lesions of the nervous system are part of a disorder which affects many tissues, though in each of these varieties the intracellular lipid material is different. On the other hand, in the various forms of cerebromacular degeneration (amaurotic familial idiocy), it is generally believed that the nervous system suffers alone. It is for that reason that two cases of amaurotic idiocy are presented, occurring in siblings, since they show some features hitherto only described in association with the generalized lipidoses.

Material

William and Annette B. are the first and second children in a family of five. Their younger siblings, male and female, not identical twins of 12, and a sister aged 7, are completely normal. Their parents are of English stock, and not related. On the paternal side, there is a general tendency to pyknic build and a high incidence of early deafness (believed due to otosclerosis) in the female members of the family. On the maternal side, psoriasis is apparently common, chiefly in the females. There is no family history of blindness, dementia, epilepsy, or other neurological disorder and no polydactyly.

Case 1.—William B. aged 19, was admitted to the Midland Nerve Hospital, Birmingham, on October 9, 1956.

His birth was normal, and his mother had been well through pregnancy. Development in infancy and early childhood was uneventful, though there was a tendency to excess weight from an early age. He walked at 13 months, and was talking by 16 months. He went to an elementary school at the age of 5, where he made average progress until he was 8, when impairment of vision in both eyes was first noticed. The latter increased, and at 9½ he had to be transferred to a blind school. By this time some intellectual decline was evident, with forgetfulness and difficulty in learning, which prevented him mastering even the rudiments of braille. When he was about 16, he became totally blind, and at the same stage his mental decay seemed to advance more rapidly. He was soon unable to dress himself, to attend to his toilet, or to feed without supervision, and he began to put on more weight. Normal conversation with him became impossible, because he seemed constantly taken up with an imaginary world. In the last two or three years his gait had gradually become abnormal and slightly unsteady, and recently he had often been incontinent in his clothes.

Mental State.—He was talkative, fatuous, and inclined to giggle excessively. He could give his name correctly and, with hesitation, his address and the day and month of his birth but not the year. It was impossible to get any account of his illness from him. He was disorientated in time and place, though sometimes he was aware of being in hospital. He could not answer the simplest questions in general knowledge, and could not add, subtract, write, or spell. He talked at random about non-existent friends, and showed other evidence of frank delusion (for instance, that his father was a doctor). He had no insight into his condition and insisted that he could see, making up descriptions of things and events he was watching. It was uncertain whether this was purely an anosognosic state, or whether he was actively hallucinated.

Physical State.—There was marked general obesity with abdominal and axillary striae, and plethoric facies (Fig. 1). Hair distribution was normal, but his beard was sparse. The external genitalia were normally developed. He was completely blind, with widely dilated pupils unreactive to light. The fundi showed fine scattered dark brown punctate pigmentation in the retinae, with optic atrophy and attenuation of the blood vessels, but no macular abnormality. There was irregular slow nystagmus in all directions of gaze. A slight defect of coordination of movement of all four limbs was present, which was not classically cerebellar, yet was not the result of proprioceptive deficit. Stance was normal, but gait hesitant, small-paced, and slightly unsteady, with arms still at his sides. His speech was slightly spluttering in quality. No other abnormal physical signs were seen. Blood pressure was 160/105 mm. Hg.

FIG. 1

FIG. 2

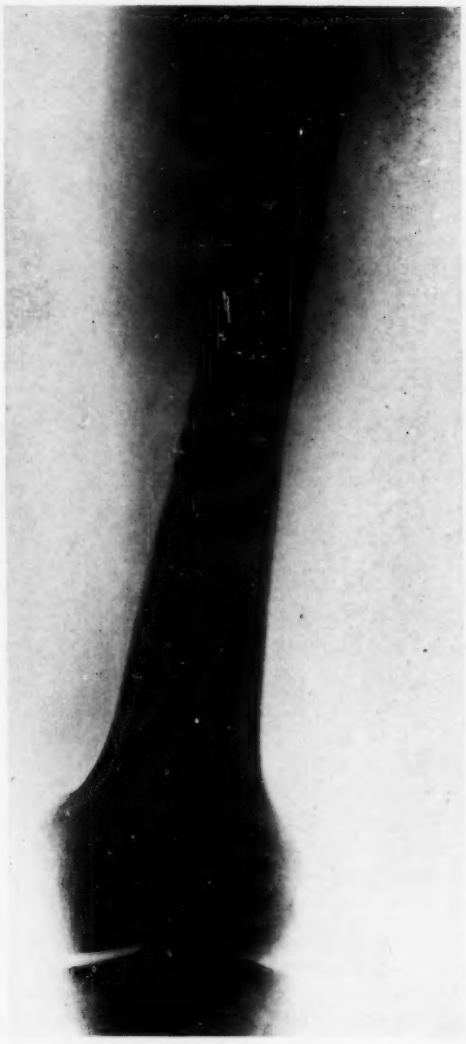

FIG. 3

FIG. 1.—Obese and plethoric appearance, with abdominal striae (Case 1).

FIG. 2.—Radiological appearance of mid and lower dorsal spine; well-marked compression and osteochondritis of vertebral bodies (Case 1).

FIG. 3.—Expansion with cortical thinning of supracondylar one-third of femoral shaft (Case 1).

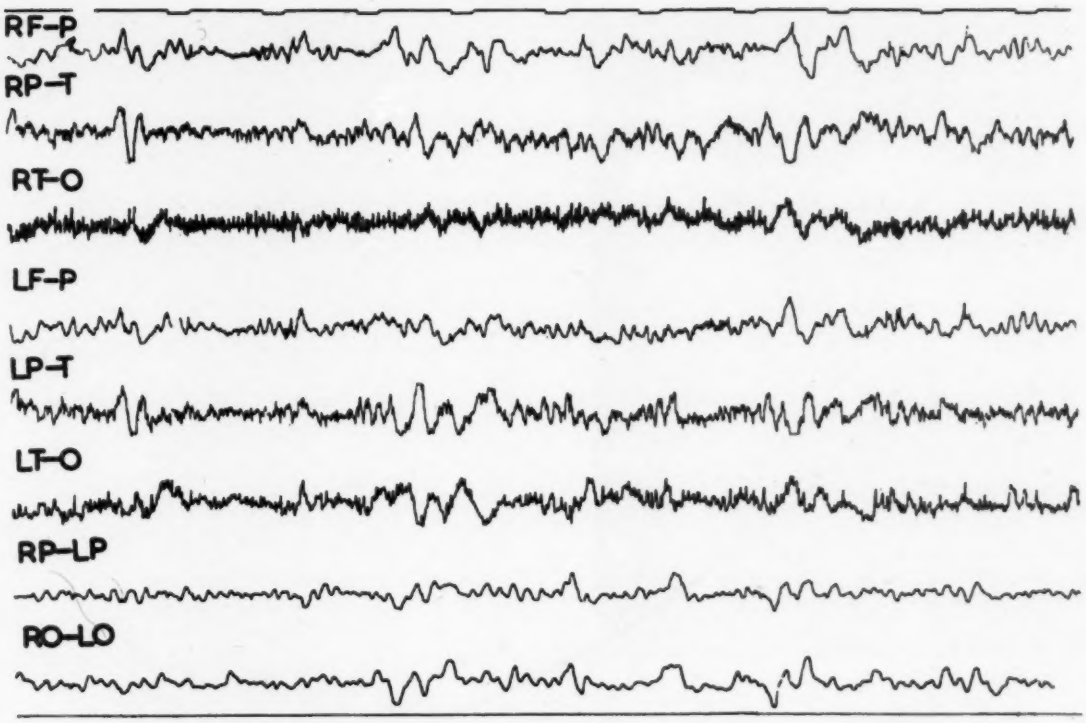

FIG. 4.—The E.E.G. of Case 1, demonstrating recurrent high amplitude transients of symmetrical pattern.

Investigations.—Radiographs of the skull and chest were normal, and those of the spine showed flattening of the thoracic vertebrae with osteochondritis (Fig. 2). Radiographs of the limbs showed slight expansion and cortical thinning of the lower ends of both femora (Fig. 3), with cortical thickening in the midshaft of the tibiae.

Generalized osteoporosis was visible in the whole skeleton.

Pneumoencephalography showed symmetrical dilatation of the third and both lateral ventricles, with pooling of air in the subarachnoid spaces.

An E.E.G. showed recurrent high-voltage, slow-wave disturbances, appearing with bilateral synchrony every 2-4 seconds. The background of the record showed an unstable alpha rhythm with a general excess of theta activity (Fig. 4).

Laboratory Studies.—(*a*) Haemoglobin was 16·2 g.% (110%), R.B.C.s normocytic and normochromic in stained films, W.B.C.s 8,500 (polymorphs 59%, eosinophils 1%, lymphocytes 36%, monocytes 4%). (*b*) The E.S.R. was 8 mm./hr. (Wintrobe). (*c*) Blood Wassermann and Kahn reactions were negative. (*d*) Serum sodium was 130 m.Eq./1, potassium 4·6 m.Eq./1, chloride ion 102 m.Eq./1, calcium 12·4 mg./100 ml. (*e*) The serum copper level was 133 μg./100 ml. and (*f*) serum iron (i) 233 and (ii) 177 μg./100 ml. (two separate estimations). (*g*) Liver function tests (two separate estimations) gave: serum albumin (i) 5·4 and (ii) 5·0 g./100 ml.; serum globulin (i) 2·5 and (ii) 2·1 g./100 ml.; gamma globulin (alcohol method) (i and ii) 1·0 g./100 ml. (ammonium sulphate method) (i) 2·2 and (ii) 2·0 g./100 ml.; zinc sulphate turbidity (i) 5·0 and (ii) 4·0 units, zinc sulphate flocculation (i) and (ii) +++; thymol turbidity (i) 2·0 and (ii) 1·0 units, thymol flocculation (i) and (ii) negative; colloidal gold (Patterson) (i and ii) 2, (Maclagan) (i and ii) negative; van den Bergh (direct reaction) (i and ii) positive, (indirect reaction) (i and ii) positive; serum bilirubin (i) 2·1 and (ii) 1·1 mg./100 ml.; serum alkaline phosphatase (i) 8·3 and (ii) 5·5 units/100 ml.; cephalin cholesterol (i and ii) negative, serum-free cholesterol (i) 90 and (ii) 60 mg./100 ml., ester cholesterol (i) 140 and (ii) 150 mg./100 ml. (*h*) Faecal fat excretion in 72 hours was 6 g. (*i*) Urinary 17-ketosteroid excretion was 6 mg./24 hr., 17-hydroxysteroid excretion 14 mg./24 hr. (*j*) Urinary amino-acid chromatogram: glycine +++, serine ++, glutamic acid +, aspartic acid trace, lysine trace, cystine +, glutamine +, arginine ++, alanine ++, valine trace, phenylalamine trace (excretion pattern probably within normal limits). (*k*) Cerebrospinal fluid pressure and manometrics normal; protein 53 mg./100 ml., globulin (Pandy) trace, (Nonne-Apelt) negative, Lange 1111000000; cytology less than 1 white cell/c.mm.; Wassermann reaction negative. (*l*) Urine no albumin or sugar.

Case 2.—Annette B., aged 16, was admitted to the Midland Nerve Hospital, Birmingham, on October 21, 1956.

Like her brother, her birth and early development were quite normal, and she walked and talked at 11 and 14 months respectively. Her eyes were examined at the age of 7, and are known to have been normal then.

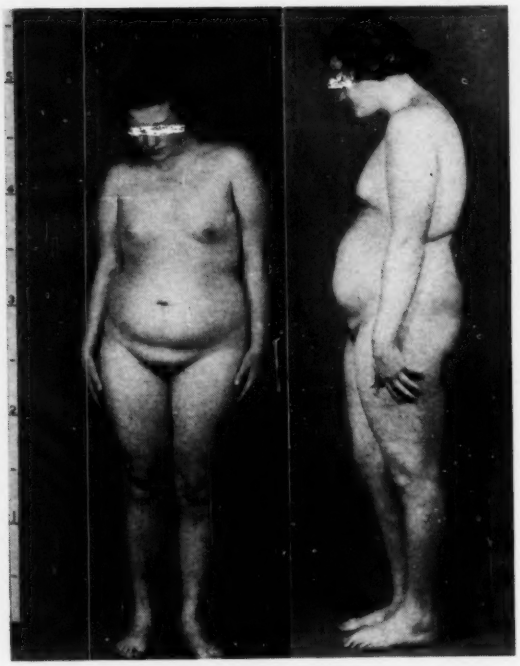

FIG. 5

FIG. 6

FIG. 7

FIG. 5.—Obesity and habitual posture (Case 2).

FIG. 6.—Radiological changes (Case 2) in lower mid-thoracic spine for comparison with Fig. 2.

FIG. 7.—Appearance of the femur, showing typical flask shape (Case 2).

However, at the age of 9 visual failure began, and had advanced sufficiently to necessitate transfer to a blind school at 11. The onset of intellectual deterioration was probably at about this time, but unlike William she was able to learn braille. She continued to be able to read it, though never proficiently, until she was 15, when it became obvious that she was increasingly forgetful and slow in comprehension. Tasks which she could manage before were now too much, and she became labile in mood, and often tearful. All the time she steadily became increasingly blind.

When she was 12, she developed a valgus deformity of the left foot. Several manipulations were ineffective, and later peroneal tenotomy was done with only partial success. About the same time she began to put on weight, and to become round-shouldered. The menarche was at 14, and the periods have been regular since.

Mental State.—She was shy and reticent, and frequently wept both during questioning and when on her own in the ward. She was correctly orientated for time and place, and had a sufficient store of general knowledge to name, for example, the Prime Minister and the capital city of Great Britain. She could spell out her name and address, and simple words of up to four or five letters, but was unable to do even the simplest arithmetic. Her power of concentration was poor, and it was impossible to get a clear account of her illness from her.

Physical State.—She was an obese girl with abdominal striae and marked dorsal kyphosis (Fig. 5). Hair distribution, breast development, and external genitalia were normal. She had left pes valgus.

Visual acuity was difficult to assess, but was probably little more than light-dark discrimination. The pupils were mid-dilated and reacted imperfectly to light. Ophthalmoscopy revealed scattered fine dark pigmentation in both retinae with attenuated vessels and somewhat pale discs. There was irregular coarse nystagmus in lateral gaze, and some defect of coordination of the limbs. Her gait was slouching, with short, cautious steps, and the arms held still. She had no other physical abnormalities. Blood pressure was 150/80 mm. Hg.

Investigations.—Radiographs of the skull and chest were normal, and of the spine showed definite mid and lower thoracic osteochondritis (Fig. 6). Those of the limbs showed the lower ends of femora to be flask-shaped (Fig. 7). The middle phalanges of the fingers were rather short, with partial fusion of the capitates and hamates. The patient had mild generalized skeletal osteoporosis.

Pneumoencephalography showed slight generalized dilatation of the ventricular system, particularly at the trigone.

An E.E.G. showed repeated slow-wave events of high amplitude similar to those seen in the brother's record, but less regular in occurrence, and tending to last longer (Fig. 8).

Laboratory Studies.—(*a*) Haemoglobin was 14·8 g.% (100%), R.B.C.s normocytic and normochromic in films, W.B.C.s 13,000 (polymorphs 80%, eosinophils 1%, lymphocytes 18%, basophils 1%). (*b*) The E.S.R. was 11 mm./hr. (Wintrobe). (*c*) The blood Wassermann and Kahn reactions were negative. (*d*) Serum sodium was 131 m.Eq./1, potassium 4·1 m.Eq./1, chloride ion 103 m.Eq./1., calcium 12·4 mg./100 ml., phosphorus 3·3 mg./100 ml. (*e*) Serum copper was 139 μg./100 ml. and (*f*) serum iron 105 μg./100 ml. (*g*) Liver function tests gave: serum albumin 5·1 g./100 ml.; serum globulin 2·6 g./100 ml.; gamma globulin (alcohol method) 1·7 g./100 ml. (ammonium sulphate method) 2·5 g./100 ml.; zinc sulphate turbidity 6.0 units, zinc sulphate flocculation ++++; thymol turbidity 2·0 units, thymol flocculation negative; colloidal gold (Patterson) 1, (Maclagan) negative; van den Bergh (direct reaction) positive, (indirect reaction) faintly positive; serum bilirubin less than 0·5 mg./100 ml.; serum alkaline phosphatase 6·1 units; cephalin cholesterol negative; serum-free cholesterol 60 mg./100 ml., ester cholesterol 80 mg./100 ml. (*h*) Faecal fat excretion in 72 hours was 19·1 g. (*i*) Urinary 17-ketosteroid excretion was 4 mg./24 hr., 17-hydroxy-steroid excretion 19 mg./24 hr., gonadotrophin excretion less than 5 mouse units/24 hr. (*j*) Urinary amino-acid chromatogram: tyrosine trace, alanine+, threonine trace, glutamic acid trace, glycine++, serine ++, aspartic acid trace, cystine trace, glutamine trace (excretion pattern normal). (*k*) C.S.F. pressure and manometrics normal; protein 24 mg./100 ml., globulin (Pandy) trace, (Nonne-Apelt) negative, Lange 1110000000; cytology less than 1 white cell/c.mm.; Wassermann reaction negative. (*l*) Urine no albumin or sugar.

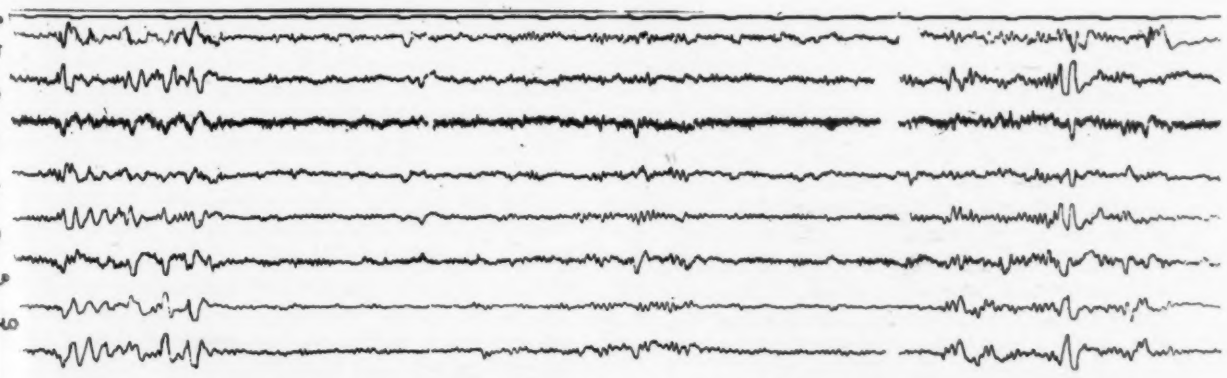

FIG. 8.—Large slow-wave interruptions in the E.E.G. of Case 2, less frequent but of more variable duration than in Case 1.

Discussion

There are two main types, one infantile and the other juvenile, of amaurotic familial idiocy, which are clinically distinct, though their underlying pathology is the same. The first is the form long ago remarked on by Tay (1881) and Sachs (1887), which comes on usually at about 3 months of age, and particularly but not exclusively affects Jews; it runs its course to death by the second or, at latest, the third year of life. Sub-variants of it exist, either congenital (Norman and Wood, 1941) or late infantile (Bielschowsky, 1914; Greenfield and Nevin, 1933) in onset. The second, and perhaps less well-known, form is that often associated with the name of Spielmeyer (1906) and Vogt (1905), though earlier descriptions were given independently by Batten (1903) and Mayou (1904) and later conjointly (Batten and Mayou, 1915). It appears between the ages of 5 and 14. It presents no racial predilection, is not marked clinically by the cherry-red macular spot so characteristic of the infantile type, the fundi showing diffuse pigmentation instead. The disease is also much slower in its evolution, and its inexorable march to mental and physical inanition covers a span of several years.

The two cases reported here are clear examples of the juvenile sort. Their ophthalmoscopic appearances are quite typical, and correspond closely with the descriptions given by earlier writers (Batten, 1903; Mayou, 1904; Nardin and Cunningham, 1923; Greenfield and Holmes, 1925; Sjögren, 1931; Norman, 1935; Dide and van Bogaert, 1938; Hoffman, 1956). The retinal pigmentation usually is macular or perimacular in situation initially, but sometimes may begin more peripherally; it is at first very fine and dust-like, later tending to become denser from coalescence of granules, and indeed the fundal appearance can finally closely resemble retinitis pigmentosa. The optic discs commonly develop atrophic change with pallor, and attenuation of the retinal arteries and veins is the rule. The macula may in some cases be discoloured. Although it is not invariable, the precedence of visual over mental changes in point of time is the usual order of events, as in our cases.

The emotional lability, impoverishment of learning and memory, fantasies, delusions, and possible hallucinations, all shown clearly in Case 1 and less floridly in Case 2, are features which match accounts of the dementing process given before (Schob, 1924; Sjögren, 1931; Marinesco, 1934; Norman, 1935; FitzJerrell and Neuchiller, 1938; Levy and Little, 1940; Lubin and Marburg, 1943; Hoffman, 1956) though they cannot be taken to represent a pathognomonic constellation in themselves.

With regard to neurological signs, pupillary sluggishness or fixity to light and nystagmus are both common at a relatively early stage or illness, and were present in our cases. It is likely that the deficient light reaction of the pupils (complete in Case 1 who was blind, and partial in Case 2) is accounted for retinal sensory ganglion cell degeneration, rather than an index of midbrain damage. The nystagmus too might be similarly explained because it had the irregular oscillatory quality, quasi searching, that may be met in the blind or near-blind of long standing. However, a cerebellar factor cannot be discounted, in view of the damage to the cerebellum which is a recognized pathological characteristic of cerebromacular degeneration, especially of its juvenile variety (Frenkel and Dide, 1913; Greenfield and Holmes, 1925; Dide and van Bogaert, 1938). Both patients also showed slight clumsiness of coordination of their limbs, and a disturbance of their gait, which looked hesitant, slovenly, and a little unsteady. It was difficult to be sure whether these were more than a simple result of lack of sight, or again significant of cerebellar deficit. However, such signs have been noticed by other writers (Greenfield and Holmes, 1925; Sjögren, 1931; Levy and Little, 1940; Lubin and Marburg, 1943), as well as the full-blown cerebellar syndrome which affected the cases of Frenkel and Dide (1913). There was no evidence of pyramidal, extrapyramidal, or sensory disorder in our cases, though an extensor plantar or mild Parkinsonian sign can occur relatively early, and in the terminal stages there may be complete general paralysis with rigidity resembling the decerebrate state. Nor had either ever had fits, though reference to the literature makes it clear that they are a common manifestation, and death in status epilepticus not an unusual event.

There are relatively few accounts of the E.E.G. changes in amaurotic familial idiocy, but slow wave (delta) dysrhythmia, with and without spikes, has been mentioned by Kornmüller and Janzen (1939), Levy and Little (1940), Lubin and Marburg (1943), and Bjelkhagen (1950). Cobb, Martin, and Pampiglione (1952) consider that the characteristic trace of the cerebral lipidoses in general is one marked by many transients of high amplitude and usually triphasic form, irregularly recurring with bilateral synchrony and diffuse distribution, together with a continuous irregular mixture of waves at 1½ to 6 c./sec., and the records of our cases correspond closely to this pattern.

The radiological findings in both patients are interesting. There is little particular comment in the literature on the radiology of amaurotic familial idiocy, such references as there are being of a negative kind, and though Levy and Little (1940), for instance, noted an abnormal spinal posture in

their case, no radiographic report was given. However, a number of radiological studies have been made in Gaucher's disease. According to Gordon (1950), bony changes in the condition were first described as a pathological entity by Risel in 1909, and later, more comprehensively, by Pick (1933); from the radiological point of view, the first complete studies were those of Klercker (1927) and Junghagen (1926). The chief signs are generalized osteoporosis, destruction and compression affecting long bones of the limbs but also the vertebrae and pelvis with formation of large and small worm-eaten defects in the spongiosa, and widening of the lower ends of the femora just above the condyles with thinning of the bony cortex. This femoral abnormality has been likened to the shape of an inverted Erlenmeyer flask and has been described by many writers as a regular, as well as an early, sign (Fischer, 1928; Welt, Rosenthal, and Oppenheimer, 1929; Reed and Sosman, 1942; Snapper, 1943), and flattening of the vertebrae with osteochondritis, though not invariable, is also a common finding. The presence of both these characteristics in the sibs reported here suggests that there may in fact be involvement of the skeletal system by lipid deposition in cerebromacular disease, just as in Gaucher's disease, and hence that there is a closer relationship between this condition and the other lipidoses than has been considered up to now.

Biochemical abnormalities have often been sought, but with little success. It is generally accepted that there may be a rise in the total protein content of the cerebrospinal fluid, with some increase in the globulin component (Levy and Little, 1940), and such was evident in Case 1, although not in Case 2. Both sibs were obese, a point which Ritter (1932), Norman (1935), and Levy and Little (1940) referred to in their examples. Both were also definitely hyperpietic for their age, and with the cutaneous striae and facial plethora as well as the obesity, their general appearance showed something approximating to a Cushing syndrome, a feature which has not been commented on by others. However, neither had other outward marks of endocrine dysfunction, and there was no deviation from the physiological in their urinary steroid excretion or (in the case of the girl) gonadotrophin output.

We were unable to detect any anomaly in their general electrolyte pattern, in their serum iron or copper levels, or signs of amino-aciduria or faulty intestinal absorption of fat. Nevertheless, in both there was an unequivocal rise in the serum gamma globulin concentration, witnessed quantitatively by the alcohol and ammonium sulphate estimations, and also by the results of zinc sulphate turbidity and flocculation tests. The significance of this phenomenon is not clear, and so far as we are aware it has not been reported before. Like the radiological signs and the Cushing characteristics, however, it suggests the existence of a bodily disorder in amaurotic familial idiocy which is not simply restricted to the retinae and central nervous system.

These two cases throw no light on the manner of inheritance of the disease, nor on its fundamental cause. It did not seem justifiable to resort to cerebral biopsy to get material for routine pathological study or histochemistry.

Summary

Two examples of juvenile familial amaurotic idiocy are presented. They were extensively investigated from radiological, biochemical, and electroencephalographic angles. Radiological changes were found in the long bones and spine not previously recorded in this disease, which correspond to those seen in Gaucher's disease, and therefore suggest that the lipid disorder may be widespread rather than restricted to cerebro-retinal neurones. Both also showed signs of Cushing's syndrome, and raised serum gamma globulin, neither reported before.

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J. Neurol. Neurosurg. Psychiat., 1958, **21**, 38.

SPINAL ANGIOMA WITH SYMPTOMS IN PREGNANCY

BY

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Spinal cord lesions of various types may produce symptoms during pregnancy. The most common cause is disseminated sclerosis, in which the association with pregnancy of both first attacks and recurrences is well known. However, recent authors (McAlpine, Compston, and Lumsden, 1955) hold that the frequency and character of this association are not incompatible with a purely fortuitous relationship between the two conditions. A much closer association of spinal cord symptoms with pregnancy may occur in angiomas affecting the cord, and it seems probable that, in some cases at least, there is a causal connexion. Three such cases are reported here.

Case Reports

Case 1 (Hosp. No. 137802) was 24 years old when first seen in the Department of Neurology at the Manchester Royal Infirmary and was then 39 weeks pregnant. Five weeks previously she had felt sensations like electric shocks down the back of her legs to the ankles, often brought on by coughing; the following week she became unsteady and later the legs became cold and numb. On examination she was pregnant and obese. There was a spastic paraparesis with increased tendon reflexes in the legs and extensor plantar responses. Sensory loss mainly to pin prick and vibration extended up to the seventh thoracic dermatome with some sacral sparing. Radiographs taken at this time showed only minor disc changes between the sixth and seventh thoracic vertebrae. Queckenstedt's test showed a partial block of the cerebrospinal fluid and the protein level was slightly raised at 60 mg. per 100 ml. Labour was induced and within a week after delivery the paraesthesiae disappeared; a month later all the abnormal signs had regressed. Three years later she again became pregnant and remained well until about 28 weeks when she felt her legs a bit heavy. At 30 weeks she noticed numbness round the abdomen and at this time slight sensory impairment could be detected with an upper limit at the eighth thoracic segment. One week later there were signs of a pyramidal lesion, and by the 35th week the sensory level had risen to the fourth thoracic dermatome. Labour was induced and within a fortnight the symptoms and signs had regressed. At this time a more thorough radiological examination showed a typical angioma of the second thoracic vertebral body; myelography

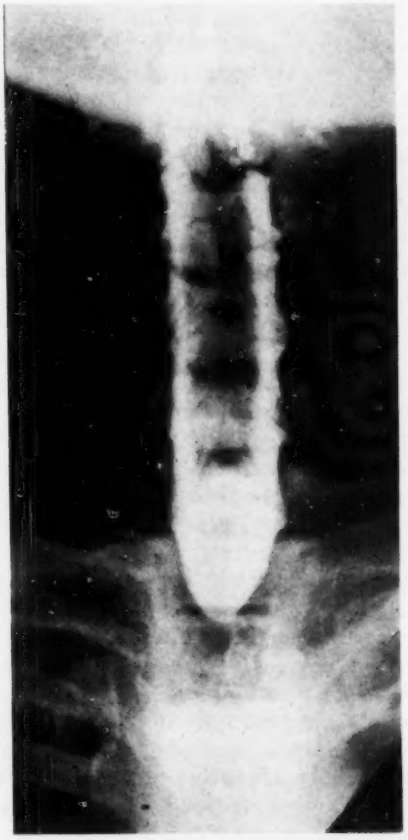

FIG. 1.—Myelogram in Case 1 to show block in subarachnoid space at the level of D.2 vertebra which has the appearance of an angioma.

demonstrated a subarachnoid block at this level (Fig. 1). For a year she continued to have slight tingling and unsteadiness of the legs, but when she was seen two and a half years after her last delivery there were neither symptoms nor definitely abnormal signs. After another year, however, symptoms again appeared and, having moved to London, she was referred to the Brook General Hospital for treatment. Mr. G. B. Northcroft performed a laminectomy on January 10, 1956, and removed an extradural angiomatous mass lying mainly in front of

the theca. She made a complete recovery and three months later was free of all signs and symptoms.

Case 2 (Hosp. No. 453/46) was aged 34. She had no symptoms until the end of her second pregnancy when she had girdle pains in the lower thoracic region; these ceased five days before delivery. She was seen in her third pregnancy, three years later in 1946. At 32 weeks the girdle pains began again, being worse when she lay down and relieved by standing; in fact she would get up and walk around when the pain came on at night. Two weeks later her legs became numb, then stiff and weak; five days before admission she became unable to walk. On examination she was 36 weeks pregnant. The legs were very weak and spastic, the abdominal reflexes were absent, knee and ankle jerks increased, and plantars extensor. There was sensory impairment, chiefly to pin prick up to the sixtn thoracic dermatome. Lumbar puncture demonstrated complete spinal block, but radiographs were not technically satisfactory. Operation was decided on; the laminae of the fourth and fifth thoracic vertebrae were found to be exceedingly vascular and the extradural space occupied by a network of dilated veins. Owing to the terrifying haemorrhage nothing further was done. The paraplegia was unchanged after operation; five days later she was spontaneously delivered, but developed paralytic ileus and died. Necropsy showed a vertebral angioma and blood clot compressing the cord; no other angiomata were found.

Case 3 (Hosp. No. 272128) was a woman of 35 who, in the eighth month of her third pregnancy, developed pain in the lower back radiating down the left leg with some weakness of this leg. One month before delivery she fell and became paraplegic with retention of urine. She had a normal full-term delivery, but there was no change in her condition until four months later. Thereafter steady improvement occurred and in March, 1952, eight months after delivery, she could walk normally. But two years later there was a recurrence of pain and hesitancy of micturition and she was admitted to the Manchester Royal Infirmary in November, 1954.

On examination, she could walk with a rather spastic gait. The bladder was distended. The tendon reflexes were normal in the arms; the knee jerks were very brisk and ankle jerks absent. The abdominal reflexes were present and the plantars flexor. There was sensory impairment over the dermatomes L.5 to S.5.

A radiograph of the spine showed an angioma of the body of L.3 vertebra. No cerebrospinal fluid could be obtained by lumbar puncture, but cisternal cerebrospinal fluid contained 140 mg. of protein. Myelography showed the typical filling defects of an intradural angioma

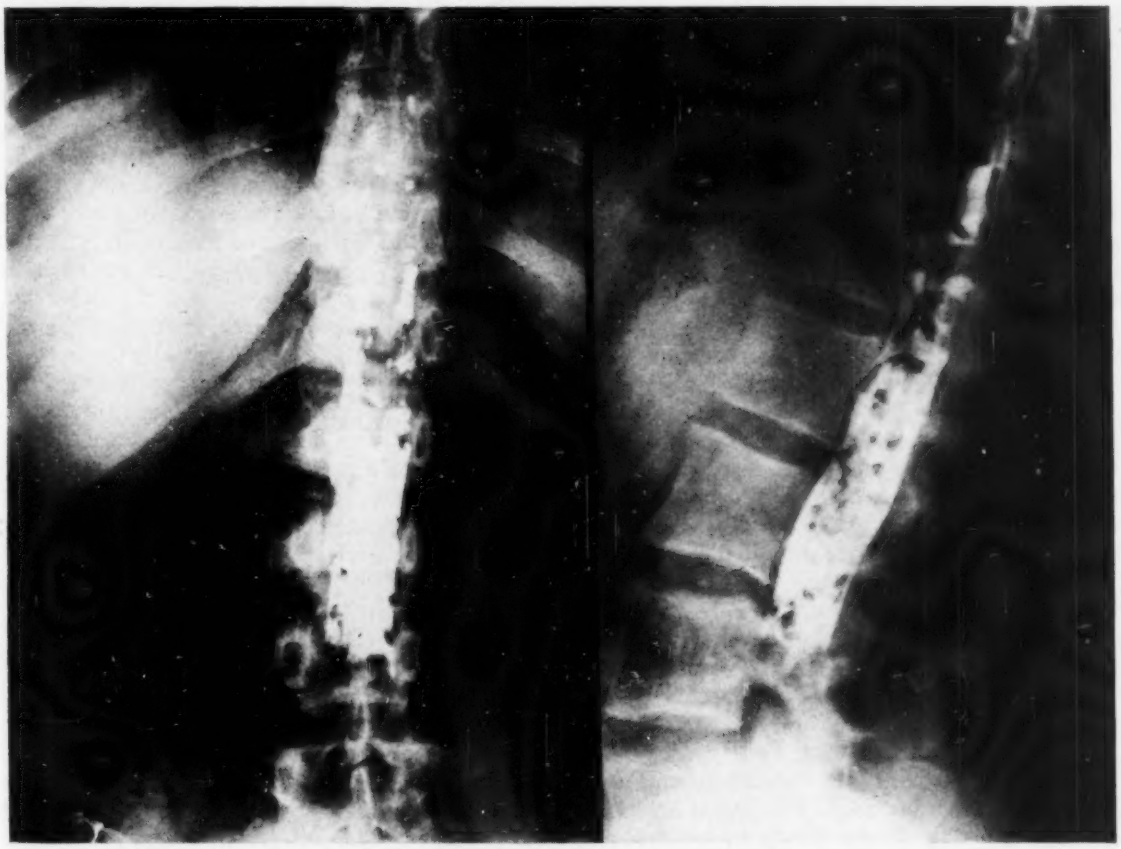

FIG. 2.—Myelogram in Case 3 to show the typical filling defects of intradural racemose angioma in addition to an angioma of the body of L.3.

between T.11 vertebra and a complete block opposite L.3 (Fig. 2).

She was given radiotherapy and control of the bladder was regained. However, by June, 1955, walking was again worse and she had periodic retention of urine. There was now flaccid paralysis of the left leg with absent tendon reflexes, and sensory impairment was detectable up to the level of T.6.

Discussion

Balado and Morea (1928) have previously recorded, in a most striking case, similar relapses and remissions due to an extradural angioma and associated closely with pregnancy. Their patient was a woman of 36 who, in the space of 10 years developed spastic paraparesis in seven out of eight pregnancies, with complete remission between. The pattern of relapse was not the same each time; there were no symptoms at all in the sixth pregnancy, while in the seventh, paraplegia came on suddenly in the last week and continued five months after delivery, and in the last pregnancy symptoms returned at the seventh month and were fatal. At necropsy, there was found an extradural tumour in the upper thoracic region composed of interwoven large and small blood vessels and cavernous spaces.

Michon, Grégoire, and Lafont (1935) describe a patient with a vertebral angioma who developed sudden paraplegia in the last month of her sixth pregnancy. Earlier in the same pregnancy and in the two previous ones she had complained of pain in the interscapular region. Radiographs showed an angioma of the fourth thoracic vertebral body and radiotherapy three months after delivery was followed by rapid improvement. Delmas-Marsalet (1941) has reported relapse and remission in two pregnancies in a case of intradural racemose angioma. The patient was a woman of 26 who, eight years before in her first pregnancy, developed pain in the neck and arms made worse by coughing and straining and eased by standing upright. Later there was some weakness of the legs but all the symptoms disappeared " as if by miracle " on delivery. A precisely similar sequence of events occurred in the second pregnancy, but three years later the symptoms recurred and progressed although she was not pregnant. Examination showed spastic paraplegia with a sensory level at the second thoracic dermatome; myelography was typical of racemose angioma with changes extending over the upper thoracic region; laminectomy showed the expected lesion, apparently venous in nature, lying beneath the dura and attached to the cord.

Other authors have reported less striking episodes: Bergamaschi (1956) in a case of vertebral angioma, Lam, Roulhac, and Erwin (1951) in an epidural haemangioblastoma and Girard and Garde (1955) and Brion, Netsky, and Zimmerman (Case 7, 1952) in intradural angiomas.

The cause of the production of such symptoms may be supposed to be due either to a direct increase in venous pressure from the enlarging uterus or to the effect of the hormones produced in pregnancy on the walls of blood vessels. Simple obstruction might well have brought about the onset in Case 3. In the other cases the lesion was in the upper thoracic region and venous drainage from the angioma must have been mainly into the superior vena cava where increase in pelvic pressure would have little effect. In Delmas-Marsalet's case symptoms began in the second month of pregnancy before any major mechanical effects could have made themselves felt. It seems more likely that an altered hormonal environment with increased circulating oestrogen and progesterone caused dilatation of the abnormal vessels and their feeding arterioles, or possibly constriction of the draining venules. A similar explanation has been advanced for the distension of varicose veins in early pregnancy and, less plausibly, for the appearance of spider naevi in liver disease. A patient personally observed had a cutaneous angioma of cavernous type on the upper trunk which enlarged in early pregnancy and returned to its previous size after delivery; a similar sequence of events is described by Davis (1938) while spider naevi frequently appear in pregnancy and disappear after delivery.

Epstein, Beller, and Cohen (1949, Case 1) and Pappenheim (1938, Case 1) have reported cases of intradural racemose angioma in which symptoms were aggravated at the menstrual periods, further supporting the hypothesis of a hormonal effect, and Johnson (1957) reports a similar occurrence in angiomas of the brain-stem. On the other hand, the relief of pain on standing in Case 2 points to the importance of simple hydrostatic factors.

While simple coincidence of symptoms with pregnancy must be considered in some cases, prompt improvement after delivery is very suggestive of a causal connexion in a condition such as vertebral angioma where spontaneous remission does not occur except post partum; recurrence of symptoms at the same level in successive pregnancies also indicates that the relation is unlikely to be merely a chance one.

The occurrence of a transverse spinal cord lesion during pregnancy should always raise the possibility of an angioma, most frequently one in the vertebral bodies or epidural space. Although these lesions are admittedly rare, those involving the vertebra are readily diagnosed radiographically and are amenable to radiotherapy; in most cases dramatic improvement takes place in a matter of weeks. Isolated epidural angiomas are seldom diagnosed

except at operation but the intradural type often shows a characteristic pattern on myelography; treatment of the latter, however, is most unsatisfactory.

I am grateful to Dr. F. R. Ferguson for permission to publish these cases and to Mr. G. B. Northcroft for details of the later progress of Case 1.

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THE NOVEMBER (1957) ISSUE

The November (1957) issue contains the following papers:—

Arteriovenous Malformations of the Brain and their Effect upon the Cerebral Vessels. Juan Carrasco-Zanini.

The Late Sequelae of Pneumococcal Meningitis. Honor V. Smith, R. M. Norman, and H. Urich.

Electro-encephalography in a Case of Islet Cell Adenoma. John Laidlaw and S. M. Rab.

Manifestations of Suprarenal Insufficiency Occurring with Pituitary Tumours. Antony Jefferson.

Neurological Manifestations in Haemangioma of the Vertebrae. H. Askenasy and A. Behmoaram.

Rapidly Progressing Dementia in Disseminated Sclerosis. J. D. Bergin.

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PULSATING EXOPHTHALMOS IN VON RECKLINGHAUSEN'S DISEASE

BY

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Unilateral pulsating exophthalmos is often due to an arteriovenous communication between the internal carotid artery and the cavernous sinus, or to an arteriovenous aneurysm in the orbit between the ophthalmic arteries and veins. Occasionally a true aneurysm of the ophthalmic artery may cause exophthalmos. Trauma to the head is a common aetiological factor, but the condition may arise spontaneously. It is not so well known that pulsating exophthalmos can occur in some cases of von Recklinghausen's disease. The underlying cause in these cases is a defect in the bony wall of the orbit which permits the direct transmission of the pulsations from the brain to the globe of the eye. In addition the intracranial contents encroach upon the orbit and give rise to a varying degree of exophthalmos. Examples of this condition have been described by R. F. Moore (1931), LeWald (1933), Wheeler (1936), A. E. Moore (1936), Pfeiffer (1943), Friedman (1944), and Peyton and Simmons (1946). Petit-Dutaillis, Feld, and Taptas (1949) were able to find only 37 references to this condition in the international literature; they added two cases of their own. Such a small number of reported cases is surprising when the voluminous literature on von Recklinghausen's disease is considered. This would suggest that the condition is either rare or that, as pointed out by Peyton and Simmons (1946), the lesion is recognized only by those familiar with the syndrome.

The cutaneous manifestations of von Recklinghausen's disease are known to be only one aspect of a congenital defect which may disturb normal development in many parts of the body. In particular, abnormalities of the skeletal system are now well known and have been reviewed by Holt and Wright (1948). The changes which may be found in the bones of the skull in this disease have been discussed by Rosendal (1938). Osseous lesions, if looked for in von Recklinghausen's disease, are common. Crowe, Schull, and Neel (1956) have expressed the view that it is only rarely a patient does not show some skeletal involvement. Defects in the wall of the orbit appear to be one of the osseous manifestations of this disease and perhaps they are more common than is at present recognized.

We have seen in the space of a few months two patients with von Recklinghausen's disease, in both of whom unilateral pulsating exophthalmos was present. *X*-ray examination of the skull revealed defects in the bony wall of the orbit in both cases. These are reported here as further examples of this interesting condition.

Case Reports

Case 1.—This was a young man, aged 26 years, with no previous history of ill-health. He was admitted to the Department of Neurosurgery, Royal Infirmary, Cardiff, on March 27, 1955. About 12 months previously he had noticed that the vision in his left eye was blurred, but this visual defect had not progressed. Six months later, while combing his hair, he became aware that his left eye was pulsating. He was certain that before this the eye had been normal except for the poor visual acuity. There was no complaint of headache, but he had occasional attacks of sharp pain, shooting in character, above the left eye. There was no subjective impression of pulsation of the eye, and there was no history of diplopia.

On examination the left eye was slightly prominent and showed definite backward and forward movement which was synchronous with the pulse. Compression of the left carotid artery lessened the amplitude of the pulsations and also caused some enophthalmos; compression of the right carotid reduced the amplitude of the pulsations only. Compression of the jugular veins increased the degree of exophthalmos. The fundi were normal; there was no engorgement of the retinal veins on the left side and the degree of venous pulsation was normal. Visual acuity on the left was impaired, but was normal on the right. The visual fields were full and external ocular movements were normal. No bruit was heard on auscultation. Neurological examination did not reveal any abnormal physical signs. He had a mild degree of generalized neurofibromatosis, as indicated by the presence of several café-au-lait spots and small violaceous cutaneous neurofibromata scattered over the trunk.

FIG. 1*a* and *b* (Case 1).—Postero-anterior and lateral radiographs showing the partial absence of the roof and the posterior wall of the left orbit.

Radiological Examination of Skull.—Postero-anterior projections showed a uniform translucency of the left orbit in sharp contrast to the normal appearances on the right (Fig. 1*a*). There were no shadows corresponding to the orbital plate of the frontal bone, or the lesser wing and orbital plate of the sphenoid bone. The oblique sphenoid line in the left orbit was absent. There was a large orbital extension of the frontal sinus on the left and the ethmoidal cells medial to the orbit were narrow. The corresponding cells on the right were large and prominent. There was no bulging of the squamous temporal bone. Lateral views (Fig. 1*b*) showed an abnormally deep pituitary fossa with a steep anterior wall which was lacking in definition. The posterior part of the roof and the posterior wall of the left orbit were absent. The right anterior clinoid process was large and pneumatized; the left anterior clinoid process was not seen. In the basal view the anterior wall of the left middle fossa was not apparent. The foramina spinosa were identified, but the other basal foramina were poorly defined on both sides. The lateral part of the body of the sphenoid was ill-defined.

The pressure of the lumbar cerebrospinal fluid was 120 mm. Manometrics, chemistry, and the cytology of the fluid were normal. The blood Wassermann and Kahn reactions were negative.

Electroencephalography.—The record showed fairly high voltage alpha rhythm at 10 c./sec. arising in the occipital lobes. Short runs at 7 c./sec. theta waves also occurred in all leads and were augmented by hyperventilation.

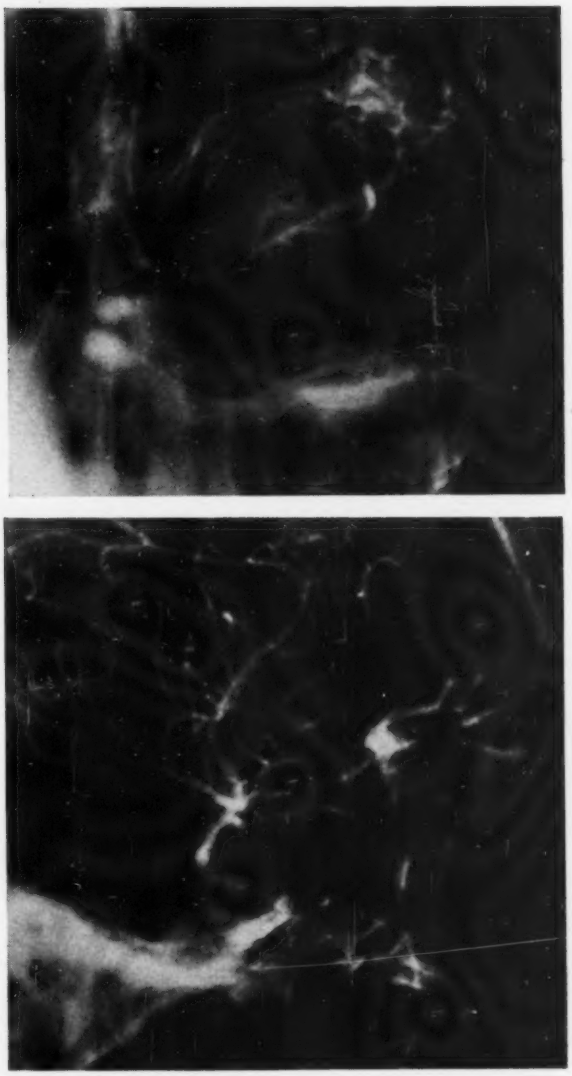


FIG. 2*a* and *b* (Case 1).—Antero-posterior and lateral angiograms showing the abnormally-shaped and medially-placed carotid siphon.

Left Percutaneous Carotid Angiography.—The carotid siphon (Figs. 2*a* and *b*) was abnormal in shape and position, lying more medially than normal. The C2 and C4 portions of the siphon were abnormally long, with the C3 portion lying well forwards. The whole siphon lay more anteriorly and medially than normal while at one point the medial border of the siphon lay 1 cm. to the right of the midline. The C1 portion of the siphon was directed upwards and laterally, the bifurcation being 1 cm. anterior to the posterior clinoids, and on a level with them. Radiological examination of the lumbar spine, the right femur, and the left humerus revealed no abnormality.

Operation.—Through a left frontal craniotomy (C.L.) performed on April 6, 1955, the anterior and middle cranial fossae were explored. The anterior fossa was small from before backwards but otherwise appeared normal. There was no evidence of tumour on the wing of the sphenoid. The left olfactory tract and optic nerve were normal in position and appearance, but the internal carotid artery was not seen. On palpating the anterior wall of the middle fossa there was a soft area about 3 to 4 cm. in diameter where the bone was deficient. This region was also explored extradurally and revealed the orbital fat presenting immediately under the dura mater.

The patient made an uneventful recovery after operation and was subsequently discharged from hospital. Periodic follow-up examinations have shown no increase in the degree of exophthalmos or pulsation.

Case 2.—This was a woman aged 34 years who was admitted to the Department of Neurosurgery on June 28, 1955. Unfortunately, owing to the patient's mental state and the fact that her husband had little command of the English language, it was not possible to obtain an adequate history, The patient, the mother of seven children, had recently left hospital after her latest confinement. About nine months before this, a progressive change in her mental state was noticed. She became apathetic and lost interest in her children of whom she was formerly very fond and of whom she took great care. She lost her personal pride, became slovenly in dress and cleanliness. She complained of frontal headache and at times was confused and disorientated. The deterioration in her mental state became so marked that she was admitted to a local hospital on June 5, 1955.

On examination she was drowsy, apathetic, and it was not possible to engage her in conversation. She had several café-au-lait spots and many cutaneous and subcutaneous neurofibromata scattered over her body. The skull was asymmetrical with a well-marked bulge in the left temporal region. The left eye was slightly prominent and on close examination pulsation of the globe could be detected, which was synchronous with the pulse. Compression of the carotid arteries and the jugular veins produced the same effects as described in the first case. The fundi were normal. A sixth nerve paresis was present on both sides and an upper motor neurone facial weakness on the left. Slight weakness was detected in the left upper limb and the reflexes here were slightly increased. Both plantar responses were extensor, but otherwise no abnormal signs were found in the lower limbs.

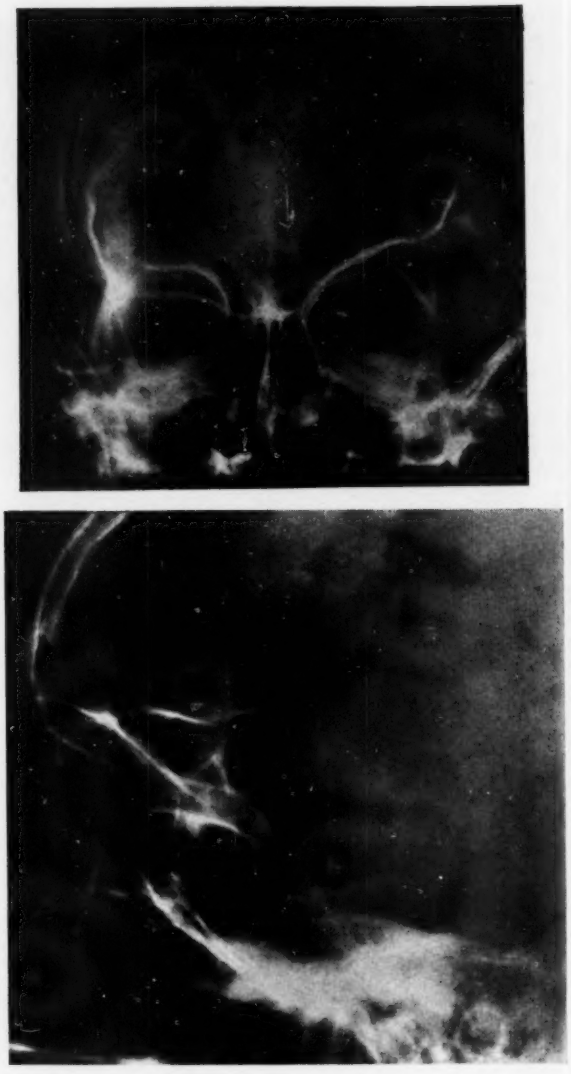
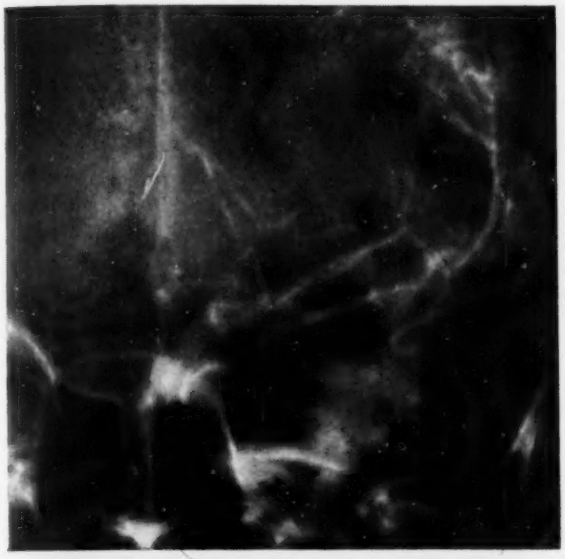


FIG. 3*a* and *b* (Case 2).—Postero-anterior and lateral radiographs to show the marked elevation of the floor of the anterior fossa and the defect in the posterior wall of the orbit on the left.

A clinical diagnosis of von Recklinghausen's disease with a right frontal tumour and congenital bone defects of the left orbit was made.

Radiological Examination of Skull.—Postero-anterior projections (Fig. 3*a*) showed that the floor of the anterior fossa on the left was very markedly elevated, particularly laterally. In the tilted P.A. view the line of the floor of the anterior fossa on the left lay above the superior border of the left orbit. The oblique line of the sphenoid in the left orbit was displaced laterally. There was well-marked outward bulging of the left squamous temporal bone. The left orbit was enlarged in all diameters when compared with the right. The normal details of the posterior wall of the left orbit were missing. The anterior clinoid process on the left could be identified and the lesser wing



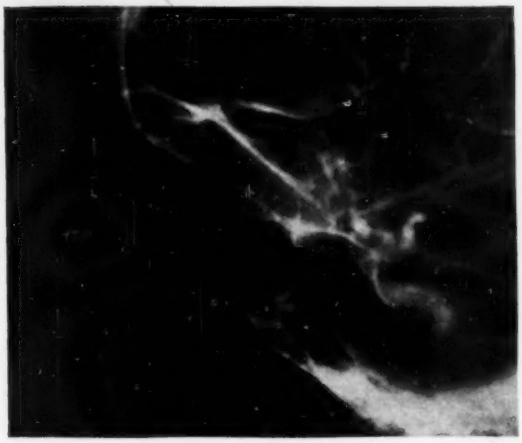


FIG. 4*a* and *b* (Case 2).—Antero-posterior and lateral angiograms to show the abnormal position of the carotid siphon.

of the sphenoid traced from this, laterally and steeply upwards to fuse with the line of the anterior fossa at and above the superior border of the orbit. In the lateral view (Fig. 3*b*) the anterior wall and floor of the middle fossa were displaced markedly forwards and slightly downwards. The sella turcica was not abnormal.

Electroencephalography.—The record showed a diffuse theta rhythm at 6 to 7 c/sec. throughout. There was very little 8 c/sec. alpha rhythm. There was no apparent focus, but the record indicated diffuse abnormality, probably indicating a deep lesion.

Left Percutaneous Carotid Angiography.—The carotid siphon (Fig. 4*a* and *b*) was abnormal in shape and position, lying more medially than normal. The medial border of the siphon reached the midline at one point. The C1 portion was directed upwards and laterally. The bifurcation lay 0·5 cm. above and anterior to the posterior clinoid process.

Subsequent ventriculography confirmed the presence of a right frontal space-occupying lesion.

Operation.—Through a right frontal craniotomy (A.D.) performed on July 6, 1955, an extensive infiltrating glioma was partially removed. Histological examination showed that the tumour was a piloid astrocytoma.

In spite of the fact that an adequate internal decompression was obtained at operation, there was no improvement in the patient's condition. She died in coma on July 20, 1955.

Necropsy.—This confirmed the clinical findings and the extent of the bone defects as shown in radiological examination. The pituitary gland was normal and there was no evidence of an intracranial or intra-orbital neurofibroma.

Discussion

Exophthalmos in cases of von Recklinghausen's disease may be due to an orbital tumour, a glioma of the optic nerve, or be the result of congenital orbital bone defects. A correct diagnosis is obviously of considerable importance. If the exophthalmos is due to congenital absence of part of the orbital wall and the true nature of the lesion is not recognized the patient may be led into an unnecessary surgical procedure. In our first patient a mistaken diagnosis of a vascular sphenoid wing meningioma was made and a transfrontal exploration carried out.

There is no doubt that these congenital defects should be suspected on clinical examination, for, as stressed by Robertson (1949), " the condition is so characteristic that a mistake is unlikely once the condition is known ". The final recognition of the disorder, however, rests on an adequate radiological examination of the skull. The appearances are distinctive and are not likely to be confused with any other condition. Contrast studies are not essential, although they may give valuable additional information. While the extent of the bony abnormality may vary from case to case, characteristically there is an absence of the bony detail in the posterior wall of the orbit due to a partial absence of the orbital plate of the frontal bone, and a similar failure in development of the greater and lesser wings of the sphenoid bone. The body of the sphenoid also is usually involved, as shown by the abnormal shape of the sella turcica. In addition the squamous temporal bone often bulges. The affected orbit is larger than normal, the ethmoidal air cells on the same side are usually narrow and the maxillary antrum small.

A point of importance in the differential diagnosis of these bone defects is their clear-cut nature, which contrasts with the ill-defined margins of bone defects produced by tumour erosion.

Contrast studies have not been reported on many of these patients. Robertson (1949) reported a case in which an orbital encephalocele was demonstrated by air encephalography. Petit-Dutaillis *et al.* (1949) and Elslo and van der Zwan (1952) have reported cases and described the findings on angiography. In both of our patients angiography was carried out and an abnormality revealed. The most striking feature was the medial displacement of the whole of the carotid siphon, which also lay more anteriorly than normal. These features were most obvious in our first case, where in addition the C2 and C4 portions of the siphon were elongated. The size of the internal carotid artery was not abnormal in either of our cases.

In the case described by Elslo and van der Zwan (1952) the carotid siphon was also abnormal in shape and position with elongation of the C2 and C4 portions. Unfortunately the relationship of the siphon to the midline was not mentioned. These appearances were interpreted as an aneurysm. The authors felt that the protrusion and pulsation of the eyeball were due to this, and that the enlargement of the sella and the bone defect of the orbit might be due to the continuous pulsation of the aneurysm and contents of the orbit. We do not think that the abnormal carotid siphon demonstrated in our cases can be classified as an aneurysm. In our opinion the bony anomaly is the primary lesion and the unusual vascular pattern a secondary manifestation of this defect. The dislocation of the carotid siphon to the midline is the result of a failure in development of the corresponding side of the body of the sphenoid, and the forward displacement, and elongation of parts of the siphon, to the absence of the posterior wall of the orbit.

It seems probable that some of these cases never develop symptoms which call for treatment and go through life without the condition being recognized. Certainly the degree of pulsation of the globe in our two cases was such that there was no subjective disturbance and the exophthalmos was slight. In Case 2 the bony anomaly was only an incidental finding in the presence of another more serious lesion. In those patients with a marked degree of exophthalmos transfrontal repair of the orbit roof, as described by Dandy (1929), would appear to be the operation of choice. However, marked or progressive exophthalmos, occurring in a patient with von Recklinghausen's disease, should call for full investigation even in the presence of undoubted congenital bone defects of the orbital wall. Intracranial tumours are not uncommonly associated with neurofibromatosis, as in our second case, and the orbital wall defect may then act as a natural decompression in the presence of a rising intracranial pressure. It is advisable, therefore, if a surgical repair of the orbital wall is contemplated, to carry out preliminary angiography or air studies.

Summary

Two cases of von Recklinghausen's disease with pulsating exophthalmos due to congenital bone defects in the orbital wall are reported.

The radiological appearances are described and the abnormality revealed by cerebral angiography is discussed.

Treatment is briefly discussed and the importance stressed of carrying out contrast studies before surgical treatment in patients with progressive exophthalmos.

We are particularly grateful to Dr. A. M. Jones for his help in the interpretation of the radiographs of these patients.

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OPTIC ATROPHY AND NERVE DEAFNESS IN DIABETES MELLITUS

BY

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The belief, once held, that an aetiological relationship exists between diabetes mellitus and optic atrophy is not now generally accepted. The observations of early authors such as Allbutt (1871) and von Noorden (1917), who regarded optic atrophy as a diabetic complication, may have been partially vitiated by the fact that both visual loss and changes in the optic discs may result from other ocular complications of diabetes and need not be an expression of primary nerve degeneration.

Waite and Beetham (1935), in a comprehensive survey of the visual mechanism in diabetes, reported optic atrophy in 27 (0·69%) of the 3,915 fundi that they were able to examine in 2,002 diabetic patients, and in four (0·44%) of the 901 visible fundi of 457 non-diabetic persons. These findings have, however, been repeatedly misinterpreted by subsequent authors (Wagener, 1938; Tunbridge and Paley, 1956) who, by overlooking the fact that the percentage figures related to individual fundi and not to patients, quote a higher incidence of optic atrophy in both groups than was actually recorded. It is not possible to derive from these data the percentage of patients in each group having optic atrophy in one or both eyes. On the basis of their findings Waite and Beetham (1935) considered the two conditions to be fortuitously associated: that no aetiological relationship exists between them is the view now generally accepted. The development of both optic atrophy and diabetes in two or more members of a family is thus of special interest.

Wolfram (1938) reported a family of eight children, four of whom, two boys and two girls, developed diabetes mellitus and bilateral optic atrophy by the age of 12. Tyrer (1943) described an 18-year-old boy who suffered from infantilism with goitre, diabetes mellitus, mental defect, and bilateral primary optic atrophy. One sibling suffered from diabetes and epilepsy and had pronounced bilateral primary optic atrophy; another, who was only 5 years old when examined, was also diabetic and epileptic and had pallor of the optic discs. A third family was reported by Tunbridge and Paley (1956) in which two members, brother and sister, were diabetic and had primary optic atrophy; they had, in addition, bilateral nerve deafness. We report here a fourth family in which the association of diabetes mellitus with optic atrophy and nerve deafness is again encountered but in which, unlike the other three, more than one generation is involved.

Report of Cases

Two of the patients are sisters, the youngest members of a family of 13, born of non-diabetic parents in whom there was no consanguinity. The third patient is the only daughter of their eldest sister who herself is not diabetic. All of these patients have diabetes mellitus and bilateral nerve deafness. Two have bilateral optic atrophy and one a neurogenic bladder.

Case 1.—Harriet N., born in 1928, is now aged 29. Her mother was aged 37 at the time of the child's delivery which was at full term after an uncomplicated pregnancy. The patient contracted whooping cough when aged 2 and measles when 3 and shortly afterwards her tonsils and adenoids were removed. At the age of 4 it became apparent that her hearing was defective and bilateral deafness has since become progressively marked. When aged 8 she was admitted to hospital on account of weight loss, thirst, and polyuria and the diagnosis of diabetes mellitus was established by the demonstration of glycosuria and impaired glucose tolerance. Control was readily achieved by dietary measures and the daily administration of small doses of insulin but since puberty it has been less satisfactory, the present requirement of insulin being 104 units.

On physical examination she is of healthy appearance and, although unresponsive and monotonous in speech because of her deafness, is not mentally backward and lip-reads moderately well. No neurological abnormality can be demonstrated apart from the deafness, and the blood Wassermann reaction is negative. The optic discs are normal and the only ocular abnormality is a true diabetic cataract in the left eye. Both tympanic membranes show minimal scarring but they are intact and quite mobile. There is no congenital malformation of external or middle ear and nose and throat are healthy. With eyes closed she is unresponsive to the spoken word. Rinné's test is positive in both ears and Weber's test shows indefinite lateralization to the left. Absolute bone conduction is markedly diminished. On audiometric examination only residual hearing is present in both ears from 500 to 1,000 c.p.s. and no bone conduction is recordable.

Case 2.—Betty N., born in 1930 prematurely, is now aged 27 years. After measles and bronchopneumonia in infancy she progressed normally until aged 9 when she started to lose weight and to complain of thirst and polyuria. Hyperglycaemia, defective glucose tolerance, and glycosuria confirmed the diagnosis of diabetes. At that time she had no abnormality of vision or hearing and the diabetes was well controlled by dietary restriction and the administration of insulin in modest daily dosage (24 units). The following year her vision was noticed to be defective and her hearing impaired. That these defects were attributable to bilateral optic atrophy and nerve deafness was established two years later and both have become progressively marked over the years. Although never having complained of urinary symptoms, she was found, when aged 17, to have a markedly distended bladder and to be capable of voiding as much as 900 ml. of urine at a time without any preceding sensation of fullness. Cystometric studies at that time showed that bladder tone remained at 15 cm. to 18 cm. throughout filling to 450 ml. and at 500 ml. voluntary contractions produced a rhythmic series of increases in tone, with an amplitude extending to 40 cm. There was no sensation of fullness throughout. No other neurological abnormality was demonstrable and the cerebrospinal fluid was normal in all respects. It was concluded that she had an atonic neurogenic bladder. The diabetes has remained well controlled, although the insulin requirement has gradually increased to 72 units daily.

She is of average build and stature and, although handicapped by grossly defective vision and hearing, is alert and not mentally backward. The bladder is distended. Visual acuity is reduced to perception of hand movements on both sides. There is bilateral optic atrophy with well-defined disc margins but no retinopathy. The ear drums are intact, unscarred, and freely mobile and there is no congenital malformation. Rinné's test is positive on both sides and absolute bone conduction is markedly shortened. On audiometric examination there is severe loss of hearing throughout the entire frequency range with no hearing above 6,000 c.p.s. and no bone conduction is recordable. Apart from these abnormalities and uniform depression of the deep reflexes the nervous system is intact. The blood Wassermann is negative and urinary amino-acid pattern normal.

Case 3.—Catherine R., now aged 13, is the only child of the eldest sister of the two previous patients. Her mother was 31 when the patient was born in 1944, the pregnancy being uncomplicated. The child's development was normal until the age of 4 when she was noticed by her parents to be hard of hearing; tonsils and adenoids were removed but without benefit. During convalescence from measles the following year, she failed to gain weight and developed polyuria, nocturia, and thirst. The diagnosis of diabetes mellitus was established on the basis of hyperglycaemia, impaired glucose tolerance, and slight ketonuria. Control was achieved by dietary restriction and the injection of approximately 20 units of insulin daily and has since been well maintained, although her daily insulin requirement has now risen to 64 units. The auditory defect has become progressively marked and the diagnosis of bilateral nerve deafness was established in 1953 when the patient was aged 9. In the last two years her vision has also gradually become defective.

She is a well developed child who, because of her disability, is unresponsive and at times sullen and difficult although not mentally backward. The otological findings are similar to those described in the previous patient and confirm the presence of bilateral nerve deafness. Her visual acuity in both eyes is reduced to 4/60: near vision to N 36. Optic atrophy with clearly defined disc margins is present in both eyes but there is no retinopathy. The nervous system is otherwise intact and the blood Wassermann reaction is negative.

Other Members of the Family

The mother of Cases 1 and 2 and grandmother of Case 3 is presently aged 62. She has no glycosuria (a single post-prandial blood glucose value was 110 mg./100 ml.) and there is no ocular or auditory abnormality. None of her six siblings, or their progeny, has or had diabetes, or visual or auditory defect. Her husband died recently in hospital from pulmonary heart disease and his case records state that the urine contained no sugar and that the optic fundi and hearing were normal. Of his 12 siblings none had diabetes but his youngest sister had an illegitimate male child, now aged 27, a high-grade mental defective, who was found to have diabetes when admitted to an institution at the age of 17. His diabetes has been well controlled by diet and insulin and examination shows no evidence of optic atrophy or nerve deafness. Nothing is known of his father or of his father's family.

The sibship, of which Cases 1 and 2 are the youngest two members, consisted of eight girls and five boys. The seventh child was prematurely born and died in the immediate post-natal period. The tenth, who was one of twins, died in hospital at the age of 3 but the cause of death was not established. The oldest of the family, now aged 44 and the mother of Case 3, has neither glycosuria nor post-prandial hyperglycaemia and her optic fundi and auditory function are normal. There is no history of diabetes in her husband's family. In the other eight brothers and sisters, who are living, and in their offspring, who number 23, there are no instances of diabetes mellitus, optic atrophy, or nerve deafness.

Discussion

The coexistence of diabetes mellitus and optic atrophy in the same individual need not imply a causal relationship and it is not suggested that the development of the ocular or auditory lesions in these patients is the consequence of the altered metabolism of diabetes. Indeed, in two of the cases recorded, the onset of nerve deafness antedated the clinical manifestation of diabetes; in one instance (Harriet N.) the interval was four years and in the other (Catherine R.) two years. Nevertheless, it is of interest and significance that a relationship between diabetes and optic atrophy should have been encountered amongst members of four unrelated families in different parts of the world and that other

features, namely, nerve deafness and neurogenic bladder dysfunction, should have been common to some of them.

Tunbridge and Paley (1956), who contrasted their own patients with those described by Wolfram (1938), expressed the view that " when there was enough well studied material, a statistical analysis might allow geneticists to distinguish biotypes within the range of hereditary optic atrophy." The importance of reporting details of family groups, in which inherited conditions occur simultaneously, was stressed by Roberts (1945). Indeed he went so far as to say that " it may easily happen that a single small pedigree may be decisive in regard to whether or not there is close or moderate linkage between the genes, thus making possible a solid contribution to the task of mapping the human chromosomes, and, if the chance is missed, so rare an opportunity may not recur for centuries ". As Crew (1947) puts it, " a storehouse of pedigrees is an essential requirement in clinical medicine ". It is from this aspect that it is considered important to study these patients in light of those previously recorded and to note the various points of contact.

The four families now recorded contained 12 diabetic members. A feature common to them all is the early age of onset of the disease. The average age at which the diagnosis was established was 7 years and in all diabetes had developed by the age of 12, although in no instance was there a high incidence of the disease among the antecedents. In the families reported by Tyrer and Tunbridge and Paley there was no history at all of diabetes in earlier generations and in each of the other two families only one diabetic relative was traced.

The presence of optic atrophy has been established in 10 of the 12 individuals under consideration. In one of the other two, Harriet N. described above, it was definitely lacking: she, however, has unilateral juvenile cataract, a true complication of diabetes. The other patient is one of the diabetic siblings of the case described by Tyrer in whom pallor of the optic discs was recorded but it is uncertain whether or not vision was impaired; the child was only 5 years old at the time of examination and there is no information as to subsequent developments. From the details available it appears that optic atrophy was of similar type in all the patients involved; none had central scotomata and in this respect and in its invariable failure to remit, the type of atrophy differs from the classically described hereditary optic atrophy of Leber.

Although less striking than optic atrophy in the frequency of its occurrence among these patients, nerve deafness is nevertheless recorded in five of them—all those of the present group and both of Tunbridge and Paley's cases. However, it is now known (Tunbridge and Paley, 1956) that three of Wolfram's patients had subnormal hearing as tested by a watch tick, although this was not recorded in his original description and the nature of the auditory defect is not known.

The last feature in this constellation of defects is neurogenic bladder atony. It may be that its occurrence in Betty N. as an isolated neurological lesion with no other evidence of myelopathy is quite fortuitous, but it is interesting to note in Tunbridge and Paley's paper their reference to the development of cord bladder in two of Wolfram's patients.

There are thus many features common to the members of those four diabetic families described to date. Despite the fact that the pattern is not identical in all cases, the overlap is sufficient to raise the possibility that they constitute a genetic entity. Tyrer inclined to the view that his original description was of a new and previously unrecorded clinical syndrome and it is suggested that the three cases here recorded may be further examples of the same genetic type.

Summary

Three members of a family are described, two sisters, and a niece, in whom the coexistence of diabetes mellitus, bilateral optic atrophy, and bilateral nerve deafness is encountered. All three conditions are present in two of them but the third member, although suffering from diabetes and nerve deafness, has normal vision. With the exception of one male relative who is diabetic, there is no history of diabetes mellitus, optic atrophy, or nerve deafness in other members of the family.

Current views on the relationship between diabetes and optic atrophy are discussed and the cases are contrasted with the three other families previously recorded in which an association between these conditions has been described.

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SODIUM AMYTAL AND EXTRAVERSION

BY

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" Extraversion " and " introversion " are descriptive terms denoting two types of behavioural reaction and personality organization widely recognized and described in psychological literature (Guilford, 1934; Eysenck, 1953). " Extraverted behaviour " is characterized clinically by the outward expression of feelings and attitudes, in words, gestures, and acts, in a spontaneous and direct manner, little impeded by reflection, indecision, or reserve. The contrary, " introverted behaviour ", comprises a tendency to limit or moderate spontaneous outward expression, reflection, preoccupation, and rumination rather predominating. A reserved or even withdrawn attitude may be maintained. While individual people may be predominantly introverted or extraverted in their behaviour, fluctuation normally occurs from one form to the other. Introducing these types Jung (1923) writes:

> " But every individual possesses both mechanisms —extraversion as well as introversion—and only the relative predominance of the one or the other determines the type." (p. 10)

And again:

> " A rhythmical alternation of both forms of psychic activity may correspond with the normal course of life . . . ."
>
> " Outer circumstances and inner disposition frequently favour the one mechanism or hinder the other; whereby a predominance of one mechanism naturally arises. If this condition becomes in any way chronic a type is produced, namely an habitual attitude, in which the one mechanism permanently dominates; not of course that the other can ever be completely suppressed in as much as it also is an integral factor in psychic activity." (p. 13)

Persistently introverted or extraverted attitudes and behaviour patterns are frequently seen in neurotic subjects; marked fluctuations occur here also.

In the course of intoxication with alcohol or a sedative drug, such as barbiturate, a shift is often seen from introverted towards extraverted behaviour. Verbal and motor expression, both spontaneous and responsive, become conspicuous in behaviour, reflection and passive experiencing minimal. A particular pattern of " uninhibited " behaviour, often at variance with the normal and conventional practice of the subject, may be a constant or recurrent response to alcohol or sedation. Attitudes may appear which are never or seldom expressed in the normal state. Strong affective expression may appear (" be released ") such as euphoria, expansiveness, resentment, anger, or depression.

During the initial stages of anaesthesia, with say ether or " pentothal ", patterns of motor activity or excitement may appear, similar to those extraverted patterns described, but usually short-lived and associated with a more definite clouding of consciousness. This activity is not constant; the majority of subjects become progressively sedated and do not show it. My own observation of many patients receiving pentothal before E.C.T. showed such initial excitement regularly in the same subjects suggesting that it may be a constant response for certain individuals.

Introverted behaviour may lessen and extraverted behaviour emerge under the influence of many other factors; each is appropriate to certain situations. However, a shift towards extraversion appears to be facilitated in certain people by drugs with a particular type of depressant action on the central nervous system.

An objective measure of extraversion (the " rathymia " or R scale; Guilford, 1940) was given to a group of introverted neurotic (dysthymic) subjects after injections of placebo and sodium amytal (Laverty and Franks, 1956). The R score was significantly higher after sodium amytal, confirming the extraverting effects of the drug. These subjects also answered the questionnaire more often in the affirmative after injections of " amytal ".

Shagass (1954) and Shagass and Naiman (1955, 1956) used sodium amytal to establish an objective measurement of sedation, " the sedation threshold". This measure, the quantity of drug (mg./kg. body weight) required to produce inflection in the amplitude of the " barbiturate-fast " activity of the electroencephalogram (a point usually concurrent with the onset of slurred speech) was found to be high for

introverted neurotics, low for extraverted and normal subjects, and intermediate for " mixed neurotics ".

> " A high sedation threshold seems to be associated with obsessional personality traits, introversion, and a predisposition to anxiety, tension, and depressive symptoms; a low threshold . . . with hysterical personality traits, extraversion, and a predisposition to conversion symptoms " (Shagass, Naiman, and Mihalik, 1956).

It may be argued from this that introversion depends on a cerebral activity which is opposed by sodium amytal (before full sedation), in the course of which opposition a shift from introversion towards extraversion takes place; the overcoming of this activity may be presumed to require a certain quantity of the drug and this could account for the higher doses necessary to produce the sedation threshold in introverted subjects. If introversion is the factor in question both neurotic and normal introverted subjects should behave in the same way, becoming more extraverted after amytal and showing a high sedation threshold. Extraverted subjects, on the other hand, should show little or no increase in extraversion and have a low threshold.

The present investigation was carried out to test these expectations.

Method

Forty subjects were tested as to their degree of " extraversion " using Guilford's R scale. Each subject was tested on two occasions, once after amytal and once after injection of a placebo. Four groups of 10 subjects tested in this way were made up as follows:

Group I. Introverted neurotic subjects
Group II. Introverted normal subjects
Group III. Extraverted neurotic subjects
Group IV. Extraverted normal subjects

The neurotic subjects were in-patients or out-patients of the Maudsley Hospital and were all complaining of current neurotic symptoms or showed neurotic disturbances of behaviour. They were selected as " introverted " or " extraverted " on the basis of their behaviour and history taken during a preliminary interview. The normal subjects were psychiatrically unsophisticated acquaintances of my own, selected as being " extraverts " or " introverts " according to their known personalities and free from a history of mental illness or neurotic symptoms. The proportion of men to women in each group (I to IV) was 6 : 4, 6 : 4, 5 : 5, 6 : 4. Ages were between 18 and 37.

The subjects were asked to participate in an experiment in which their experience of the passage of time would be tested after the injection of a drug: such a test was given after each injection but does not form a part of the investigation reported here.

Amytal injections were given in the manner described by Shagass *et al.* (1956). Sodium amytal solution, freshly prepared, in a dose of 0·5 mg./kg. body weight/ml. sterile water, was injected at a rate of 1 ml. in 40 seconds. At 40-second intervals the subject was requested to read a sentence on a card held before him and from this response the onset of slurring of speech was assessed. At this point the injection was stopped.

Placebo injections of sterile water were given in the same way.

After the patient was able to sit up and walk about comfortably, and did not appear to be drowsy, the Guilford R scale was presented in the form of cards. The subject was requested to sort the questionnaire cards into boxes labelled " Yes ", " ? ", and " No ", answering them according to the way he felt at the time.*

A random order for the administration of placebo or amytal at the first or second session was prepared and followed for each group. The subject's behaviour and mental state before and after injection was assessed and recorded. No positive suggestions with regard to symptoms were given. All the verbal comments made by the subject during the card-sorting tests were recorded as giving an indication of the presence and quantity of spontaneous talk.

Results

These are reported as follows: (1) Questionnaire scores; (2) spontaneous talk; (3) symptoms reported; (4) behaviour observed; (5) sedation threshold.

(1) **Questionnaire Scores (R Score, " Yes " Score, " ? " Score).**—The mean scores for each group after injection of a placebo may be assumed to be little different to what they would be without injection since placebo injection and " no treatment " scores were not significantly different in the former investigations (Laverty and Franks, 1956).

Mean R scores for the introverted groups (I and II) were: after placebo 22·8 (S.D. 3·3)† and 24·8 (S.D. 4·5); after amytal these groups showed higher R scores than after placebo, the means being 29·6 (S.D. 3·4) and 26·3 (S.D. 7·9). The extraverted groups (III and IV) showed higher R score means than the introverted groups as follows: after placebo 46·1 (S.D. 5·3) and 46 (S.D. 8·3); after amytal 48·9 (S.D. 5·8) and 48·1 (S.D. 4·5).

There is a consistent increase in the R score after amytal, being for each group (I to IV) 6·8 (S.D. 3·3), 1·5 (S.D. 3·4), 2·8 (S.D. 4·8), and 2·1 (S.D. 4·5). The difference is highly significant for the introverted neurotic group (I) at the 0·1 level of confidence. For the other groups (II to IV) the differences are not significant, but if the scores are combined, significance at the 2·5% level is obtained.

" Yes " scores (the number of cards placed in the " Yes " box) after placebo showed lower means for introverted subjects: group I, 44·2 (S.D. 13·4),

*In the former investigation (Laverty and Franks, 1956) the number of " Yes " answers was significantly increased after amytal. In the present investigation questions 8, 16, 18, 19, 57, 106, 110, 118, and 119 were put in their negative form, bringing the possible number of " Yes " responses to 43 and the " No " responses to 42.

†Standard deviations for means given in brackets.

group II, 47·9 (S.D. 10·9) than for extraverted subjects, group III, 57·0 (S.D. 12·5), group IV, 54·0 (S.D. 7·7). An increase in the " Yes " score after amytal occurred in each group, being for group I, 7·1 (S.D. 9·4), group II, 3·6 (S.D. 10·0), group III, 4·0 (S.D. 3·0), and group IV, 2·4 (S.D. 3·3). The difference is significant for the introverted neurotic group at 2·5% level, but not for the other groups. Similarly " ? " scores (number of cards placed in the " ? " box) showed a tendency to decrease after amytal as compared with placebo, but the scores being small and frequently zero the differences are insignificant. However, the number of subjects in each group showing a decrease is high for the introverted groups (10 in group I, eight in group II), and lower for the extraverted groups (five in group III, five in group IV).

(2) **Spontaneous Talk.**—Spontaneous talk during the card-sorting test was greater (number of words recorded) for extraverted groups both after a placebo and amytal. After amytal an increase in spontaneous talk was recorded for all groups, particularly for groups I and III, the mean increase being for each group I to IV 65·5 (S.D. 56), 14·9 (S.D. 126), 46·0 (S.D. 115), 17 (S.D. 47). Introverted subjects showing a restriction in speech became noticeably more talkative after amytal, often showing a sudden flow of spontaneous talk during injection.

During the card sorting subjects who had received amytal tended to read the questions aloud or to themselves, moving their lips. After a placebo this was noted only in four subjects, two in each extraverted group. After amytal it was more common for subjects to break off from the card sorting to speak directly to the investigator.

(3) **Current Symptoms Reported.**—Symptoms were reported spontaneously or elicited by questioning at each interview. Thirteen of the neurotic subjects (eight in the introverted group, five in the extraverted group) described symptoms as troublesome most or all of the time; the other seven described definite fluctuations in degree and persistence. Two subjects in the introverted normal groups and one in the extraverted normal group described feelings of anxiety.

Relief from symptoms was frequently reported after amytal. This was most evident in the introverted neurotic group; placebo injection seldom afforded relief. The neurotic introverted group reported relief after amytal from pain and somatic discomfort (7), anxiety or depression (4), recurrent or obsessional thoughts (4), depersonalization (1), and other symptoms (3). The neurotic extraverted group reported relief from pain and somatic discomfort (4), anxiety (3), and other symptoms (3). Introverted subjects described relief more often than extraverted subjects; extraverted subjects described exacerbation more often than introverts. Exacerbation of previously reported symptoms was more common after placebo than after amytal; after amytal drowsiness and dizziness were more commonly complained of, but this was transient except in two subjects who both belonged to the extraverted neurotic group.

The only introverted neurotic subject who failed to report relief from at least one symptom experienced a compulsive fear that he would commit some indiscretion under the influence of the drug. He remained anxious about this after both injections.

Attitudes.—Besides differences in reported symptoms certain alterations in attitudes were observed after amytal. These were not consistently enquired for, but in five subjects were sufficiently striking to record. A dysthymic patient who had consistently expressed anxious solicitude for a married woman with whom he was involved, after amytal abused her for compromising him. A second dysthymic subject went to a dance on the evening after injection of amytal and surprised those who knew him by his sociable attitude; formerly in hospital he had been persistently shy. A third dysthymic patient went out with her friends the day after injection of amytal; one reported " she was brighter than she ever was before, she read our fortunes out of cups—I never knew her to do that before." A fourth dysthymic subject after injection of amytal displayed for the first time in hospital a markedly paranoid attitude. A tense, extraverted patient with an hysterical weakness of the arm became excited and aggressive towards the doctor after amytal and the weakness was no longer apparent; he was previously overtalkative but polite.

(4) **Behaviour Observed.**—Abnormal behaviour patterns were noted at each interview.

Repetitive tension movements (tapping, fidgeting, etc.), restlessness or restricted movements with the appearance of tension, were noted, particularly in the introverted neurotic group; these signs were associated with complaints of tension or anxiety, and appeared relieved after injection of amytal in all the dysthymic subjects except one. Anxious behaviour of this type was seen to a lesser extent in the extraverted group of neurotics and was rather less consistently relieved after amytal. Other individual items of symptomatic behaviour in the extraverted group were unrelieved after amytal in five cases (abnormal gait, aphonia, facial tic, weakness of leg, anaesthesia), but relieved in two (retching, weakness of arm). Both these latter patients appeared relieved of anxiety, one after abreaction.

Overtalkativeness after amytal was frequently noted, often with euphoria or other affective display and in one case with motor excitement and aggressiveness. This latter patient had shown similar behaviour after alcohol on at least three occasions.

A tendency to fall asleep after the injection was observed in two subjects in the extraverted neurotic group; in other subjects drowsiness was frequently reported at an early stage in the injection but passed off to reappear transiently at about the onset of slurred speech but not lasting more than a few minutes after the injection and not reappearing after testing had begun. Three subjects felt " more alert," " more wide awake " after amytal (two in group I, one in group II).

Three other minor observations on behaviour in the introverted neurotic group may be mentioned. Three of these subjects showed an incapacity to carry out different actions simultaneously; movements of the hands, breathing, speaking, shifting, and so on were performed separately while other actions were temporarily suspended. This breaking up of the normal rhythm of movements was associated with a general restriction of movements, with feelings of anxiety or tension and was never seen after amytal, when these subjects became relaxed. Subsequent questioning showed these subjects to be very conscious of movements normally carried out unattended.

The same subjects and one other in the introverted neurotic group and one in the introverted normal group were observed to cease breathing during the time that they were reading and considering the questions on the cards; respiration was resumed with a deep inspiration as they placed the card into the appropriate box. This, and other examples of intermittent hyperpnoea were not seen after amytal; even yawning was rarely observed in this group.

Restricted and hesitant talk in three subjects of the introverted neurotic group was associated with prefatory inarticulate sounds (" Er-er ") and then failure to talk. It was noted that a remark or even a slight movement on the doctor's part immediately caused the patient to make another verbal response, often with a movement of the subject's hands or body. Following this response the patient became stuck again, unable to utter and restricted in movement. This did not occur after amytal.

No consistent relief from abnormal behaviour was noted after a placebo.

(5) **Sedation Threshold.**—The " sedation threshold ", as assessed by the point of onset of slurring of speech, was in some cases difficult to ascertain. Other changes in speech, such as slowing, drawing out of vowels, alteration in pitch, and mumbling, were noted, sometimes preceding definite slurring. Speech which was not quite clear at one point was sometimes distinct at the next. Certain subjects spoke slowly, carefully endeavouring not to slur when aware of the tendency to do so. However, a decision as to the point at which slurring occurred was made in each case.

Mean sedation thresholds (mg./kg.) for each of the four groups were: Group I, 6·4 mg./kg. (S.D. 4·0), group II, 6·1 (S.D. 3·7), group III, 4·15 (S.D. 3·5), group IV, 5·25 (S.D. 5·1). Differences between means for all groups of 10 (I to IV) are not significant. The combined means for the introverted groups I and II (20 subjects) are 12·5 (S.D. 3·9) and for the extraverted groups III and IV (20 subjects) 9·4 (S.D. 4·4). The standard error of difference for these means, 1·33, is less than half the difference between means (3·1), indicating a significant difference at the 5% level. Combining the means for the neurotic groups (I and III) and the normal groups (II and IV) does not show a significant difference between means, the difference being only 0·8.

Conclusions

Administration of sodium amytal intravenously to the point at which speech becomes slurred was associated with consistent differences in responses to questionnaires and behaviour as compared with the same observations following injection of a placebo. After amytal " R " scores, " Yes " scores (Guilford), and " number of words spoken " were higher than after the placebo; " ? " scores were less. These differences were most significant in the introverted neurotic (dysthymic) group of subjects. This group also showed a consistent relief from symptoms and from " introverted behaviour patterns ". The neurotic introverted group and the normal introverted group require a larger mean dose of amytal to produce slurred speech (sedation threshold) than the extraverted groups.

Discussion

Brazier (1954) has presented a hypothesis for the mode of action of barbiturates on the central nervous system based on electroencephalographic evidence in animals and human subjects. Brazier describes three phases of barbiturate action: (i) An initial action is exerted on neurones in the cerebral cortex (based on findings with depth electrodes in human subjects). (ii) At a slightly deeper level of narcosis

> " barbiturates appear to have a differential depressant action on a subcortical inhibitory system, the result being an augmentation of response in the non-specific sensory system that carries ' Forbes secondary responses '."

Brazier continues:

> " the phenomenon suggests a release effect, as though at *this stage* of barbiturate anaesthesia some inhibitory system, possibly in the diffuse ascending system (of the reticular substance) had been put out of action by the drug, thereby releasing from control the responses carried rostrally from this system. Such a concept envisages that there would be in normal circumstances a condition of balance between inhibition and activitation and that by increasing very gradually the depth of anaesthesia the action of the one (inhibition) can be depressed before the other."

The augmentation of this cortical response to sensory stimulus is maximal in the pre-motor area. The suggestion that it is analogous to the K-complex (Davis, Davis, Lomis, Harvey, and Hobart, 1939; Gastaut, 1953) is contested (Roth, Shaw, and Green, 1956).

(iii) At a deeper level still the differential action on inhibitory and activating systems is lost and the sole remaining activity is the " barbiturate burst ". At this stage the subject is drowsy or asleep.

It is tempting to relate the first two of these three phases to the initial stages of early barbiturate anaesthesia observed here. The first subjective report during amytal injection is usually of dizziness, warmth, or other slight sensation and occurs after 50 to 150 mg. The group of changes that follows appear related to the shift towards extraversion; relief from anxiety experiences and preoccupation, increased talkativeness and readiness of affective motor expression. The change of attitude that occurs at this point appears to be the same as underlies the differences to questionnaire responses; the subject feels less inhibited, more spontaneous, says " Yes " more often and is less indecisive (low " ? " score); the observed behaviour gives a similar impression. The terms used by Brazier to describe the altered E.E.G. in the second phase serve to describe the form of altered behaviour response also: " inhibition " is reduced, " activation " is unimpeded. The alteration is smooth in most cases, but when abreaction and abrupt excitement occur the impression of a " release effect " is obtained.

The larger sedation threshold shown by the introverted subjects confirms the findings of Shagass and Naiman (1956). Possibly the extra quantity of the drug is used in overcoming greater inhibitory activity of the kind referred to above. That the neurotic introverted subjects showed more shift towards extraversion in response to the questionnaires and in behaviour may suggest that in this group the inhibitory mechanism is more labile and associated with and sustained by anxiety.

As portrayed by Jung (1923), introversion and extraversion are two forms of personality organization and expression between which a fluctuating balance or equilibrium is maintained. At a certain stage of amytal sedation shift of this equilibrium appears, in the direction of extraversion. As described by Brazier, barbiturate anaesthesia at a certain point causes a shift in the equilibrium normally maintained between two discharging ascending neuronal systems in the central nervous system. Further study is required to discern how closely these two effects of barbiturate are linked and how far their similarities can be pursued.

Summary

Injections of sodium amytal and placebo were given to 40 subjects divided into four groups of 10 (neurotics, normals, introverts, extraverts): scores on Guilford's R scale (extraversion) were higher after amytal than after the placebo. Changes in reported symptomatology and behaviour were noted. The sedation threshold, as measured by the onset of slurred speech, was highest for neurotic introverts and this group showed the most marked changes towards extraversion. A possible physiological basis for the shift towards extraversion after amytal is proposed.

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A CONTROLLED TRIAL OF METHYL PHENIDATE (RITALIN) IN THE TREATMENT OF DEPRESSIVE STATES

BY

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α Phenyl α piperidyl acetic acid methyl ester hydrochloride (methyl phenidate, " ritalin ") has recently been introduced as a central nervous system stimulant. Animal experiments have shown that it increases psychomotor activity and has a pressor effect. Its effectiveness in counteracting the effects of hypnotics in man, experimentally and in cases of poisoning, has been reported, as has its usefulness in treating reserpine-induced depression. It has also been used in other depressive states where its action was considered to be beneficial in reducing the disorder of mood and in increasing confidence and speed of activity (Meier, Gross, and Tripod, 1954; Heiss, Becker, Hiltman, and Honsberg, 1956; Ferguson, 1955; Geller, 1955; Stier, 1955). None of these conducting clinical reports so far has utilized controls, and this paper describes a " blind " trial in which, in addition to general out-patient management and supervision, two comparable groups of depressed patients were given either the drug or a placebo over a period of four weeks.

Selection of Cases

All the patients treated were suffering from mild or moderately severe depressive reactions. Cases were selected by the following criteria: (*a*) Complaint of depression as a prominent symptom; (*b*) evidence of depression at interview, *e.g.* sad, careworn expression, general bearing, and lack of spontaneity.

In addition, all patients showed four or more of the following abnormalities: (*a*) Sleep disturbance; (*b*) loss of appetite and weight; (*c*) impairment of interests; (*d*) lack of confidence; (*e*) reduced alertness; (*f*) retardation or agitation.

Care was taken to exclude from the group cases where the anxiety component was sufficiently large to contraindicate stimulant medication or where symptoms of a physical nature were prominent.

Method

Sealed envelopes were prepared containing the prescription of placebo or methyl phenidate (10 mg. tablets) and were thoroughly shuffled. The placebo tablets were identical in appearance with the active tablets. The psychiatrist and patient were thus unaware of the true nature of the tablets the patient received during the course of the trial.

Each patient was examined at an initial interview and the actuarial data, diagnosis, prognosis rating, etc., and the results of the modified Minnesota multiphasic personality inventory (M.M.P.I.) (Hathaway and McKinley, 1951), the Kent oral intelligence test (Kent, 1946), and an adapted Porteus maze test (Porteus, 1952) recorded. The initial prescription of 1 tablet b.d. was then given.

The patient was seen again after a maximum period of a fortnight and the dose of tablets raised from 1 b.d. to 2 b.d. if improvement was not evident.

The patient was seen a third time after four weeks and after neutral conversation the psychiatrist entered his rating of the results of treatment. The patient was then asked to rate his own improvement and was finally retested with the M.M.P.I. and the Porteus maze test.

Group Matching.—Forty-five cases were treated in all. Of the 23 control patients, none failed to complete treatment. Of the 22 drug-treated cases, two failed to return. Observed, therefore, over one month were 23 control patients and 20 drug-treated patients.

The groups corresponded closely in their sex distribution, age, civil state, personality type, precipitating factor, duration of illness, type of treatment given previously and concurrently, intelligence as measured by the Kent oral test, prognosis as estimated by the psychiatrist, and depth of depression as measured by the version of the M.M.P.I. devised by the authors (Table I).

The personality type was defined as obsessive or hysteroid according to which characteristics predominated. Obsessive characteristics were excessive cleanliness, orderliness, conscientiousness, vacillation, submissiveness, and lack of confidence. Hysteroid characteristics were over-demonstrativeness, impulsiveness, changeability, exhibitionism, and a tendency to vivid phantasy.

The prognosis rating was, after Davies and Shepherd (1955), simply based on a three-point scale from 1, indicating the best prognosis, to 3, indicating the worst.

The Kent oral test is a rapid clinical intelligence test. The examiner puts a number of questions ranging from, " What are houses made of ? " or " What metal is

TABLE I

COMPARISON OF TREATMENT AND CONTROL GROUPS

	Drug	Placebo	Probability
Sex			
Male	4	10	n = 1
Female	16	13	$x^2 = 1{\cdot}74$
			P ≏ 0·2
Civil State			
Single	4	4	
Married	14	16	
Widowed, separated, or divorced	2	3	
Age			
< 20	1	3	
21 – 30	5	3	
31 – 40	6	7	
41 – 50	5	3	
51 – 60	2	6	
60 +	1	1	
Mean age in years	37·5 ± 11·5	39·5 ± 13·9	t = 0·49
			P = 0·6
Duration of Illness			
3 months	8	9	
4 – 12 months	5	6	
13 months	7	8	
Mean duration in months	12·3	13·9	
Precipitant			
Social (finance, housing)	6	4	n = 2
Interpersonal (marital, death)	5	12	$x^2 = 3{\cdot}35$
Physical (health, menopause)	9	7	P ≏ 0·2
Personality			
Predominantly hysteroid	6	10	n = 1
Predominantly obsessive	14	13	$x^2 = 0{\cdot}53$
			P ≏ 0·5
Modified M.M.P.I.			
Score	83·9 ± 4·5	81·9 ± 12·3	t = 0·67
			P = 0·5
Kent Oral Test (2 *untested in each group*)			
Mental age in years	11·5 ± 2·1	11·9 ± 2·0	t = 0·29
			P = 0·8
10	5	4	
11 – 13	10	13	
13	3	4	
Prognosis			
1	16	11	n = 2
2	3	8	$x^2 = 3{\cdot}44$
3	1	4	P ≏ 0·2
Previous Treatment			
In-patient	3	3	
Out-patient	8	12	
None	9	8	
Concurrent Treatment			
Night sedation	13	15	
No night sedation	7	8	

attracted by a magnet ?" to "Give me the names of four large cities" or "Name some birds". The raw scores of the four sub-tests (1, 3, 4, and 5) are added in two combinations (1, 3, and 4, and 1, 4, and 5) and from a scale the mental age may be derived.

To support the clinical judgment, a numerical estimate of the degree of depression was obtained using the depressive scale of the Minnesota multiphasic personality Inventory. Fifty-nine cards which constitute the depressive scale were extracted from the total of 550 which make the full test. Each card contains a statement of which examples are: "I seldom worry about my health", "I am happy most of the time", and "I cannot understand what I read as well as I used to". In the full test the patient is asked to sort these statements into three groups: "True", "False" and "Cannot Say". The "Cannot Say" group was not used in the modified test in order to limit the number of indefinite responses so that the part-test should not be invalidated. The cutting line of normality in the full test is a score of 70, scores above this being regarded as abnormal. The modified test was tried on 11 controls of whom none scored over 70 (mean score 53·3 ± 7·7), while of 45 patients, 39 scored over 70 (mean score 84·1 ± 14·3) ($t = 6{\cdot}71$; $P = < 0{\cdot}01$). Five patients later rated as "much improved" had a mean score of 60·0 ± 7·7, 18 as "improved" had a mean score of 73·7 ± 15·6, and 17 as "not improved" a mean score of 81·5 ± 12·7. (Comparing "much improved" and "improved" $t = 1{\cdot}83$, $P > 0{\cdot}05$; comparing "improved" and "not improved" $t = 1{\cdot}12$, $P = 0{\cdot}3$; comparing "much improved" and "not improved" $t = 3{\cdot}35$, $P = < 0{\cdot}01$).

To show whether the drug had any demonstrable effect on speed of performance, a set of Porteus mazes was used with the alternative paths blocked so that the subject merely had to trace a line as quickly as possible, avoiding the sides of the maze.

Results of Treatment

The results of treatment were assessed by (1) a rating scale administered by the psychiatrist; (2) the patient's rating of his own condition (in the rating scales a 5-point scale was used with +2 much improved, +1 improved, 0 no change, −1 worse, and −2 much worse); (3) re-testing with the M.M.P.I. and, (4) the Porteus maze test was repeated.

As has been remarked, of the 23 control patients none failed to complete treatment. Of the 22 cases treated with methyl phenidate, two failed to return at all. Three further cases failed to complete one month of treatment. Two of these three cases abandoned the drug because of ill-effects, primarily increased tension, one because she felt no effects from the tablets and thought them superfluous.

The results in the 40 patients who completed treatment are shown in Table II.

The results of the psychiatrists' ratings were added to give a sum in each case. These sums were written out in rank order and the median obtained. The number of methyl phenidate-treated cases and placebo-treated cases scoring more than and less than the median is given in Table II. Those scoring more than the median were assessed as "good results" and those less than the median as "poor results". The patients' symptom ratings were dealt with in the same way. The difference in time between the first and second maze performance was expressed as a percentage of the first performance and finally also dealt with as above, being classified as "speeded up" or "not speeded up or slower"

TABLE II
RESULTS OF TREATMENT IN DRUG-TREATED AND CONTROL GROUPS

	Drug					Placebo					Result
General Improvement	+2	+1	0	−1	−2	+2	+1	0	−1	−2	
Psychiatrist's rating ..	3	7	7	0	0	2	11	10	0	0	
Patient's rating	5	8	1	3	0	4	11	7	1	0	
Depression											
Psychiatrist's rating ..	2	7	8	0	0	3	11	10	0	0	
Patient's rating	5	5	5	2	0	4	12	6	1	0	
Symptomatic Improvement											
Psychiatrist's rating:											
Retardation	0	5	11	1	0	1	7	13	2	0	
Confidence ..	2	7	8	0	0	2	8	12	1	0	
Alertness ..	1	2	14	0	0	0	3	20	0	0	
Range of interests ..	2	7	8	0	0	1	10	12	0	0	
Patient's rating:											
Sleep ..	3	7	6	1	0	4	5	14	0	0	
Confidence ..	3	4	9	1	0	1	8	12	2	0	
Alertness ..	1	10	6	0	0	0	6	16	1	0	
Range of interests ..	1	12	4	0	0	2	8	13	0	0	
Sum of Symptom-sign Ratings											
Psychiatrist's rating:											$n = 1$
Good result		10					13				$\chi^2 = 0{\cdot}02$
Poor result ..		7					10				$P \triangleq 0{\cdot}8$
Patient's rating:											$n = 1$
Good result		10					12				$\chi^2 = 0{\cdot}18$
Poor result ..		7					11				$P \triangleq 0{\cdot}7$
M.M.P.I. Re-test											
Scoring less than the median score of both groups		7					12				$n = 1$ $\chi^2 = 0{\cdot}47$
Scoring more than the median score of both groups		10					11				$P \triangleq 0{\cdot}5$
Mean score and S.D.		79·0 ± 9·9					73·6 ± 13·2				$t = 1{\cdot}38$ $P = 0{\cdot}2$
Mean reduction from original score ..		−4·9					−8·3				
Porteus Mazes											
Speeded up ..		7					13				$n = 1$
Not speeded up or slower ..		10					10				$\chi^2 = 0{\cdot}8$ $P \triangleq 0{\cdot}3$

(Table II). The M.M.P.I. scores were also placed in rank order and the median obtained.

It will be seen that methyl phenidate in doses of 10 to 20 mg. b.d. was no more effective than the placebo in its general effect on the patient, in the treatment of the depression, and in the treatment of other symptoms, and that methyl phenidate did not produce any speeding up of performance on the modified maze test.

Summary

A controlled trial of methyl phenidate was undertaken on 45 patients. The patients in the treatment and control groups were shown to be comparable. Two patients abandoned the drug because of unpleasant side-effects and three others did not complete the month's treatment period. In the remaining 40 patients, methyl phenidate, in doses of 10 to 20 mg. b.d., was shown to have no advantage over a placebo in the treatment of depression or associated symptoms and no increase in rate of performance was demonstrated with the drug. As well as clinical assessments, the patients were tested with a number of quickly performed tests which may have value in standardizing the results of out-patient studies.

We wish to thank Dr. R. Strom-Olsen and Dr. Henry Wilson for permission to publish, Dr. A. K. Pittman of Messrs. Ciba Laboratories Ltd. for supplies of methyl phenidate and placebo and other help in organizing this trial, and the pharmacists at the various hospitals at which the trial was carried out—Miss A. R. M. Foulds, M.P.S., Messrs. W. S. Hodgson, M.P.S., C. R. Wiseman, M.P.S., D.B.A., D. C. Phillips, M.P.S., H. W. Bartless, M.P.S., R. Bird, M.P.S.—for their careful co-operation throughout.

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EPINEPHRINE METABOLITES AND PIGMENTATION IN THE CENTRAL NERVOUS SYSTEM IN A CASE OF PHENYLPYRUVIC OLIGOPHRENIA

BY

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The biochemical lesion associated with mental deficiency in phenylpyruvic oligophrenia is a failure of an enzyme system in these individuals to hydroxylate phenylalanine to tyrosine (Jervis, 1953). The biochemical ramifications of this single genetic loss are vast, but as yet no direct evidence has been forthcoming which specifically relates the appearance of the biochemical abnormality to the mental deficiency. Phenylalanine (Jervis, Block, Billing, and Kunze, 1940) and phenyllactic acid (Goldstein, personal communication) have been shown to accumulate in the blood and other tissue fluids and a variety of aberrant aromatic metabolites have been demonstrated in the urine (Woolf, 1951; Armstrong and Robinson, 1954; Boscott and Bickel, 1953). The light hair and fair skin which has been noted in a large majority of these patients suggest that melanocyte tyrosinase is competitively inhibited by the phenylalanine and the related abnormal metabolites. This suggestion gains support from recent publications which show that these patients maintained on synthetic diets deficient in phenylalanine manifest considerable pigmentation of the hair (Armstrong and Tyler, 1955). Further support for this mechanism appear from studies *in vitro* which demonstrated competitive inhibition of plant (Dancis and Balis, 1955) and mammalian (Miyamoto and Fitzpatrick, 1957) tyrosinase by phenylalanine and its associated abnormal aromatic metabolites.

The recent finding that patients afflicted with phenylpyruvic oligophrenia have low epinephrine plasma levels (Weil-Malherbe, 1955) suggests a further interference with enzyme systems concerned with aromatic amino-acid metabolism. This observation led us to examine the effects of phenylalanine and the associated aromatic acids on the tyrosinase activity of human phaeochromacytoma homogenates and on the D.O.P.A. decarboxylase activity obtained from beef adrenal medulla. We found tyrosinase activity to be inhibited by phenylalanine (Fellman, unpublished observations), whereas D.O.P.A. decarboxylase activity was not affected by phenylalanine, but was inhibited by phenylpyruvic and phenyllactic acids (Fellman, 1956).

We have recently had the opportunity of examining post-mortem tissue of a 14-year-old patient who died with phenylpyruvic oligophrenia†, and it is the results of these pursuits which shall be given below. Two areas of aromatic amino-acid metabolism were investigated. The aromatic amino-acids which give rise to epinephrine and the pigmentation of certain cells of the central nervous system, the substantia nigra and the locus coeruleus.

Methods

Epinephrine Intermediates.—The glands were obtained two hours after death, quick frozen, and maintained at −20° until used. The gland was ground in a mortar with acid-washed sand and 50 ml. of 0·01 N HCl. The homogenate was centrifuged at 800 x/g. for 20 minutes to remove debris and sand and recentrifuged at 25,000 x/g. for half an hour to remove finer particles. The supernatant was used for the fluorometric (Lund, 1949) and biological (Burn, Finney, and Goodwin, 1950) estimation of epinephrine and norepinephrine. Eighteen millilitres of the supernatant were lyophilized and taken up in 0·9 ml. of 0·001 N HCl and used for identification of amino-acids and aromatic intermediates in the gland by paper chromatography. For most chromatographic analysis, Whatman one part, butanol four parts, acetic acid one part, water five was used; however, occasionally butanol 600 parts, formic 50 parts, water 50 parts was used as a solvent to establish homogeneity of the isolated spots. The components of the extract were isolated by paper chromatography. A band of gland extract was permitted to separate in butanol, acetic acid, and water; one edge of the chromatogram was cut, developed with ninhydrin, and, with this as a guide, fractions were obtained by cutting crossways to correspond with the developed strip. These fractions were eluted with 15 ml. of 0·001 N HCl, lyophilized, and rechromatogrammed. In the case of tyrosine and methionine, admixture experiments were run with the corresponding radioactive

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†The pathological report is to be published elsewhere.

amino-acids to establish identity by the coextensivity of radioactivity and colour. Carbon^{14} radioactivity was determined by scanning with an end window counter.

Histochemical.—The brain was removed approximately two hours after death and fixed in 10% formalin. Sections were cut from paraffin blocks 15μ thick and stained either with toluidine blue or with the protargol-silver method of Stotler (1951) to reveal argentophilic material.

Results

Adrenal Gland Extracts.—The extract of the gland contained 425γ epinephrine/g. gland and 7γ norepinephrine/g. gland estimated by a modified fluorometric method of Lund. Normal adult values for the pressor amines are 209γ/g. gland adrenaline and 31/g.γ gland noradrenaline (Shepherd and West, 1951). The biological assay employing the rat uterus and rabbit ileum indicated a concentration of 434γ epinephrine/g. gland while the concentration of norepinephrine was so small that accurate estimation of this material was difficult with this method. Both pressor amines were detected with a paper chromatographic technique (Table I); however, our experiences indicated that very little norepinephrine was present, corroborating our other methods.

TABLE I

CHROMATOGRAPHIC IDENTIFICATION OF EPINEPHRINE AND NOREPINEPHRINE IN ADRENAL GLAND

	Rf (BAW)	Ninhydrin	Diazo Sulph.	$NaIO_3$
Epinephrine	0·30	Blue violet	Violet	Pink
Unknown No. 5	0·31	Blue violet	Violet	Pink
Norepinephrine	0·22	Blue violet	Violet	Violet
Unknown No. 5	0·22	Blue violet	Violet	Violet

The identification of three amino-acids which appear in the gland is given in Table II and Table III.

TABLE II

CHROMATOGRAPHIC IDENTIFICATION OF TYROSINE IN ADRENAL GLAND

	Rf (BAW)	Ninhydrin	Diazo Sulph.	Radioactive Tracer
Tyrosine	0·37	Blue	Orange	Coextensive with colour
Unknown	0·37	Blue	Orange	Coextensive with colour

TABLE III

CHROMATOGRAPHIC IDENTIFICATION OF METHIONINE AND PHENYLALANINE IN THE ADRENAL GLAND

	Rf (BAW)	Ninhydrin	Diazo Sulph.	Radioactive Tracer
Methionine	0·40	Red	—	Coextensive with colour
Unknown No. 7	0·41	Red	—	Coextensive with colour
Phenylalanine	0·55	Blue violet	Grey (fluorescent)	—
Unknown No. 9	0·56	Blue violet	Grey (fluorescent)	—

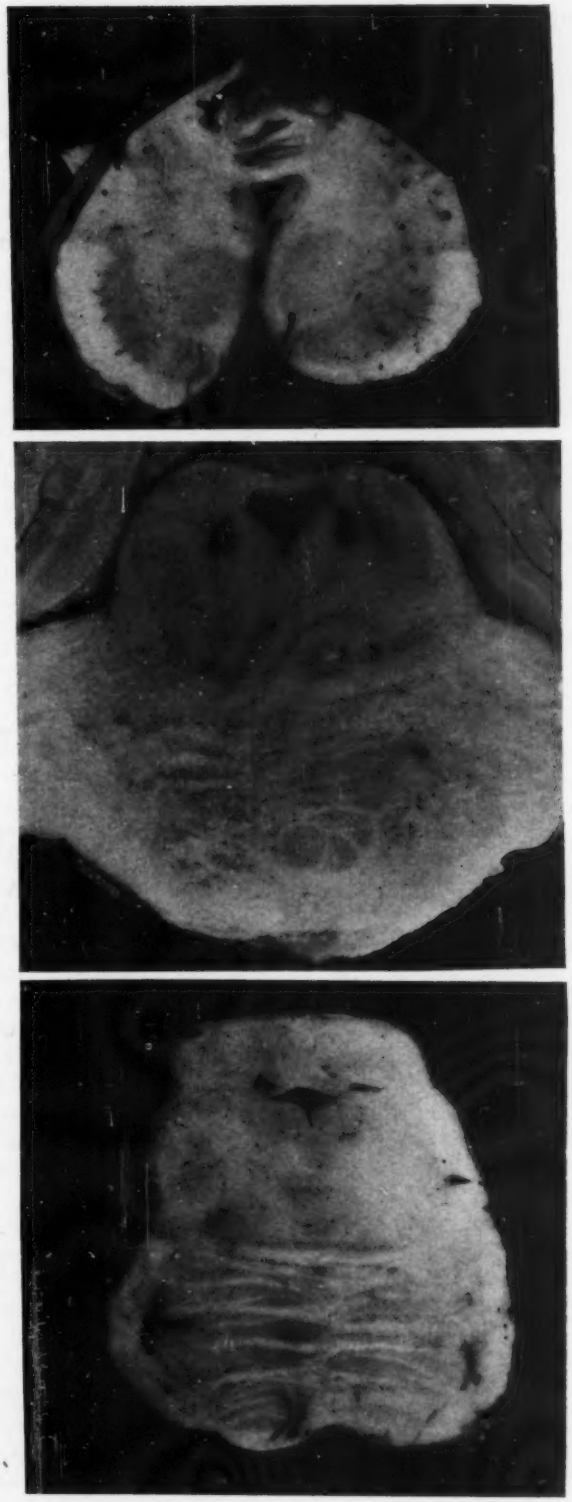

FIG. 1.—Cross section through the midbrain (upper photograph) of the case discussed, showing unpigmented substantia nigra.

Cross section through fourth ventricle (middle) of the case discussed, showing unpigmented locus coeruleus.

Cross section through fourth ventricle (lower) of norma individual showing pigmented locus coeruleus.

Their concentration in the gland was estimated from the intensity of ninhydrin colour and was in the order of 150γ tyrosine/g. gland, 900γ phenylalanine/g. gland, and 200γ methionine/g. gland. It should be mentioned that the concentration of phenylalanine determined in the blood of this patient one month before death by the method of Kapeller-Adler (1932) was 53 mg.%.

Pigmentation of Cells of Substantia Nigra and Locus Coeruleus.—Hypopigmentation of the substantia nigra and locus coeruleus was evident in gross sections (Fig. 1). When sectioned and stained with toluidine blue these areas revealed an absence of pigment granules (Fig. 2, *B*, *D*), however, Nissl's bodies were clearly evident. Sections treated with the protargol-silver procedure revealed small intracellular argentophillic granules which will be discussed below (Fig. 2, *A*, *C*). Cells from a normal individual stained with both toluidine blue (Fig. 2, *F*) and protargol-silver (Fig. 2, *E*) are shown for purposes of comparison.

Discussion

The adrenal gland of man and other animals normally contains free phenylalanine (Fellman, unpublished observations). Tyrosine and methionine do not appear to be present except in certain disease states. We have detected these amino-acids in the case discussed as well as in two other pathological states, one involving a child of 4 who died of a neuroblastoma primary to the adrenal. At necropsy massive secondary invasion of the liver and other tissue was observed. The second case was a 50-year-old adult who died in hepatic coma with cirrhosis of the liver. In both conditions free phenylalanine, tyrosine, and methionine could be detected in the adrenal gland. However, the amino-acids could also be detected in blood and in other tissue, probably as a result of liver failure and general metabolic derangement.

The accumulation of tyrosine may result from the inhibition of adrenal tyrosinase by the appearance of abnormally high amounts of phenylalanine in phenylpyruvic oligophrenia. A similar mechanism may account for the appearance of this amino-acid in the adrenal glands of the other conditions mentioned. Common to all three disease states is the appearance of free circulating phenylalanine. The appearance of methionine in these extracts may relate to its methylating functions in this gland. The high ratio of epinephrine to norepinephrine indicates, however, that methylation of the latter to the former does take place.

The examination of pigment formation in the cells of the substantia nigra and locus coeruleus clearly indicates an absence of the melanin material.* The substantia nigra is an area of the midbrain part of the extrapyramidal system, the cells of which in man, primates, and certain other mammals normally contain a melanin pigment (Brown, 1943). The functional significance of the locus coeruleus is unknown. Like the substantia nigra, pigment formation begins at the age of 4 years and continues steadily throughout life (Adler, 1942). Other investigators report pigment granules in the locus coeruleus at all ages, even in the seventh month of foetal life while in the cells of the substantia nigra pigment granules have not been observed until the eighteenth month of life (Foley and Baxter, 1956). Little is known about the mechanism of melanin formation in these cells. The formation of melanin in the melanocytes of the skin and hair matrix has for some time, however, been understood as resulting from the oxidative polymerization of tyrosine by the tyrosinase in these cells (Kukita and Fitzpatrick, 1955). These series of enzymatic and non-enzymatic alterations of tyrosine produce an insoluble black-brown pigment which is believed to be bound by primary chemical bonds to a protein of the cell (Serra, 1946). From what has already been stated in this paper about the derangement of skin and hair pigmentation in phenylpyruvic oligophrenia, do our observations of hypopigmentation in the cells of the central nervous system in this disease indicate that tyrosine oxidation is responsible for melanin formation in the central nervous system ? One cannot assume that this necessarily follows.

First, while skin and hair matrix tyrosinase is lacking in human albinos (Kukita and Fitzpatrick, 1955), normal pigmentation of the substantia nigra is observed in this genetic anomaly (Foley and Baxter, 1956). Since the embryological origin of both the skin melanocytes and the central nervous system is the neural crest, we might expect that if the same enzyme were involved a genetic loss would be reflected to wherever this enzyme occurred.

Secondly, the failure to demonstrate D.O.P.A. oxidase activity in the substantia nigra (Foley and Baxter, 1956) and the demonstration of this enzyme in melanocytes further suggests that tyrosine oxidation to melanin is not the mechanism for pigment formation in the central nervous system.

What, then, is the substrate for the elaboration of pigment in the central nervous system ? An attractive possibility is that this pigment represents a pressor amine melanin, that is, a melanin formed from the oxidative polymerization of either epine-

*In a pathological report of a case of phenylpyruvic oligophrenia, brief mention was made of hypopigmentation, namely, " The nerve cells of the substantia nigra appear to contain rather small amounts of pigment " (Corsellis, 1953).

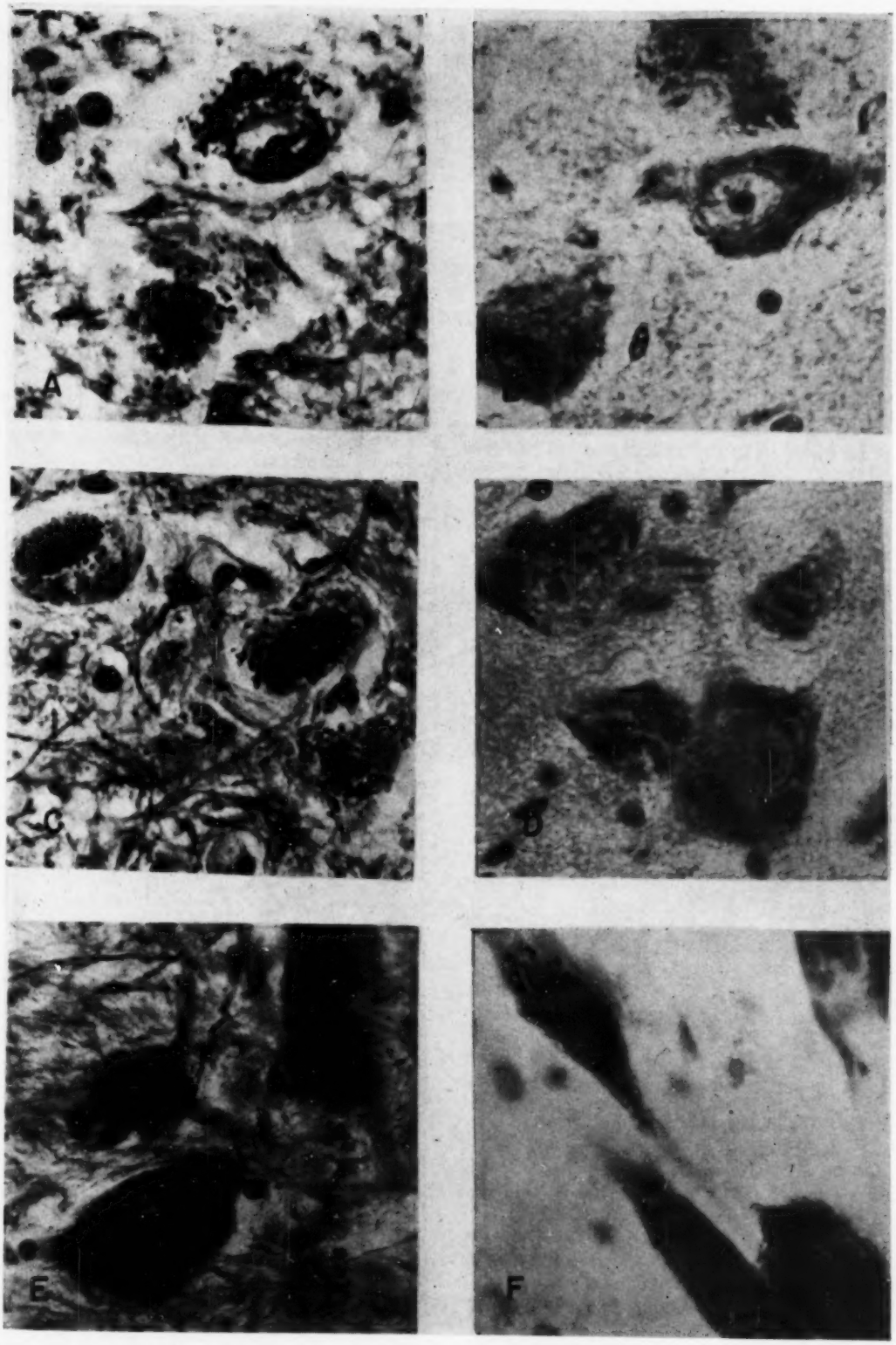

FIG. 2.—*A*. Cells of the locus coeruleus from case discussed stained with protargol-silver.

B. Cells of the locus coeruleus from case discussed stained with toluidine blue.

C. Cells of the substantia nigra from case discussed stained with protargol-silver.

D. Cells of the substantia nigra from case discussed stained with toluidine blue.

E. Cells of the substantia nigra from normal individual stained with protargol-silver.

F. Cells of the substantia nigra from normal individual stained with toluidine blue.

phrine or norepinephrine. We have some support for such a view. This would represent a useful mechanism for elimination of the pressor amine, a detoxification *in situ* as it were, and would account for the accumulation of pigment over the life span of the animal. The argentophillic granules may represent precursors of pigment formation in the substantia nigra. We have observed this argentophillic material in young, unpigmented cat and rat substantia nigra cells. These argentophillic granules are not unlike those observed in adrenal medulla and other chromaffin sites.

We may mention in passing that the accepted function for pigmentation in the skin relates to its ability to absorb harmful wavelengths of light. Surely this is not its function in the central nervous system.

The evidence presented in this paper points to two additional areas of aberrant aromatic amino-acid metabolism in phenylpyruvic oligophrenia: (1) Epinephrine biosynthesis in adrenal tissue, and (2) pigmentation of the cells of the central nervous system. With these observations we implicate alteration of metabolism in the central nervous system which probably results from the initial biochemical lesion in this disease. Obtaining from this also is the attitude that the cause of the mental deficiency associated with this genetic deficiency probably stems not from an intoxication by phenylalanine *per se*, but rather a distortion of a mutually interdependent system of aromatic metabolism leading to bizarre metabolic products and inhibition of vital biochemical pathways.

Summary

Two sites of aromatic amino-acid metabolism were examined in post-mortem material from an individual who died with phenylpyruvic oligophrenia – the adrenal gland and pigment cells in the central nervous system.

The adrenal extracts contained epinephrine, norepinephrine, tyrosine, methionine, and phenylalanine. Extracts from normal adrenal glands contain epinephrine, norepinephrine, and phenylalanine.

The cells of the substantia nigra and locus coeruleus did not contain pigment.

The implications of these observations to the disease and to pigment formation are discussed.

The author wishes to express his sincere thanks to Dr. Louis Lino, Miss Mary K. Devlin, Dr. Philip Suver, and Dr. William Stotler for their assistance and participation in this work.

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PROCEEDINGS OF THE SOCIETY OF BRITISH NEUROLOGICAL SURGEONS : 56th MEETING

The 56th meeting of the Society of British Neurological Surgeons was held in London on November 15 and 16, 1957. The Society met at the London Hospital on November 15, with the President, W. R. Henderson (Leeds), in the chair and held a combined meeting with the Association of British Neurologists on November 16 at the National Hospital, the two Presidents, W. R. Henderson (Leeds) and Sir Charles Symonds (London), occupying the chair in rotation.

On Certain Tumours of the Third Ventricle

D. W. C. NORTHFIELD (London) discussed certain aspects of a group of intrinsic tumours invading the anterior part, or the whole, of the third ventricle. Rathke pouch tumours, pituitary tumours, colloid cysts, basal ganglia tumours, and those restricted to the posterior part of the third ventricle were excluded.

Amongst 17 such cases a group emerged in which emaciation had been pronounced. It comprised six infants aged (when first seen) 1 year 4 months to 3 years 6 months. In two older patients (16 years and 21 years) loss of weight was commented upon, but in one child of 3 years and two of 8 years with tumours in this situation wasting was not found.

Skeletal growth had not been affected and some of the six infants were above average in length. Appetite at times had been voracious. In due course other neighbourhood symptoms (diabetes insipidus, loss of vision) and symptoms of raised intracranial pressure developed with enlargement of the head. Examination usually revealed optic atrophy with or without papilloedema and often little else abnormal in the central nervous system.

Skull radiographs in some showed separation of the sutures and enlargement of the sella turcica. Investigations might reveal depression of adrenal function. Ventriculography and craniotomy had confirmed the site and nature of the tumours which in the infants had been astrocytomas. Where palliative treatment had prolonged life for several years, the emaciation was gradually replaced by obesity but the child remained blind and mentally defective with varying degrees of other neurological deficit.

Case Report.—N.S. (Case No. 6906) was referred by Dr. Alex Russell for a diencephalic syndrome of wasting. The child was normal until the age of 2½ years when he began to waste away though growing normally; he had occasional headache and vomiting. At the age of 3 years height was 39¾ in. and weight 28 lb. There was slight excess of hirsutes; vision and skull radiographs were normal. An air encephalogram was normal except for imperfect filling of the anterior extremity of the third ventricle. In the next two years he grew nearly 2 in. but gained only 4 lb. in weight; thereafter he became obese. At the age of 8½ years, after minor trauma to the head, there was rapid failure of vision and a return of the headache and vomiting. Readmitted to hospital, height was 49½ in., weight 61½ lb. He was obese, the trunk hairless, and the genitalia diminutive. There was bilateral papilloedema and optic atrophy; he was nearly blind. Radiographs showed evidence of raised intracranial pressure and a large sella. Ventriculography showed dilated ventricles and an obliterated third ventricle. This was followed by an exploratory craniotomy. The child died later and necropsy showed a massive piloid astrocytoma filling the third ventricle.

Growth Hormone : New Prospects

A. STUART MASON (London) discussed new prospects with regard to growth hormones. It was noted that growth hormone, prepared from cattle pituitaries, had never produced significant protein anabolism or growth in humans. Even pure bovine growth hormone, first isolated by Li and Evans in 1944, had proved very potent in rats but not in man. This led to the suggestion that primate pituitary growth hormone was a different substance to the bovine hormone. Knobil and Greep (1956) demonstrated that growth hormone prepared from monkey pituitaries caused protein anabolism in the monkey, whereas bovine growth hormone was ineffective. Li and Papkoff (1956) obtained a pure preparation of monkey and human growth hormone and found that they were different substances to the bovine hormone. Both monkey and human growth hormones were polypeptides with a molecular weight of about 26,000 compared with 46,000 for bovine growth hormone. Raben (1957) prepared growth hormone from human and monkey pituitaries, getting a rather high yield from the former. Using these preparations on a dwarf, with a craniopharyngioma, Beck, McGarry, Dyrenfurth, and Venning (1957) obtained marked protein anabolism with concomitant calcium retention.

His present investigations recorded the effects of growth hormone, prepared from human pituitaries by Professor F. G. Young. Five milligrams were injected on two successive days into a dwarf aged 19 years, height 4 ft. 2 in. with panhypopituitarism due to a craniopharyngioma. Average daily nitrogen retention over five days from the first injection was 2 g. Sulphur and phosphorous retention was in the same proportion to nitrogen as found in protoplasm. There was a short period of increased urinary calcium loss. Salt and water retention occurred for five days, followed by a diuresis. Potassium

was retained for two days. Storage of sodium and potassium was not consistent with an A.C.T.H.-like effect. Serial radio-iodine uptakes showed no change, indicating the absence of T.S.H. from the preparation. A slight drop in urinary chloride concentration and no rise in urinary specific gravity indicated no contamination by posterior lobe hormones.

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Follow-up of Cerebellar Astrocytomas in Relation to their Pathology

J. V. CRAWFORD, L. J. RUBINSTEIN, and D. S. RUSSELL (London) presented a follow-up study of cerebellar astrocytomas in relation to their pathology. The post-operative fate of 60 cases when correlated with the micro-scopical structure of the tumour indicated that these tumours were divisible into two groups.

The first, which could conveniently be called "juvenile", accounted for about 80% of their pathological material of 70 cases and arose in early life. The mean age of the group was 9 years. Long survival, up to 20 years or longer, was the rule even when only part of the tumour had been removed (seven cases). Microscopically this juvenile form was of the kind frequently labelled as " polar spongioblastoma "; it was, however, composed of stellate astrocytes as well as piloid cells and should be regarded as a form of astrocytoma. Occasionally, recurrence of growth demanded further operation and, in one such example, evidence of anaplasia was noted in the recurrence. Vascular endothelial proliferation and invasion by the tumour of leptomeninges had been observed in several instances when only part of the tumour had been removed; nevertheless, these patients still survived after long periods.

The second type was of " diffuse " character, comparable to the cerebral astrocytomas and was uncommon (12 cases). These mostly arose in adults, the mean age being 24. Of the eight examples followed up, five died soon after operation. Like the cerebral astrocytomas they were prone to undergo anaplasia (six cases). In two further patients who died shortly after operation the appearances were indistinguishable from those of glioblastoma multiforme.

" Recurrent " Medulloblastoma

CAMPBELL CONNOLLY (Birmingham) discussed the problem of recurrent medulloblastomas. A review of the literature indicated that a few cases of cerebellar medulloblastoma (Bailey, 1930; Lampe and MacIntyre, 1954; Penfield and Feindel, 1947) after being treated in the first instance by operation and deep *x*-ray therapy, developed obstructive hydrocephalus without the recurrence of a large growth. Three such cases were described. In these, there was a small amount of viable tumour tissue in the cerebellar vermis and this showed evidence of degeneration due to the irradiation. However, in each case the obstruction at the outlet of the fourth ventricle was due to the formation of fibrous and glial tissue rather than to tumour. It was considered more likely that this collagen and glia formed as a result of the irradiation than as a reaction to the tumour.

It was therefore suggested that ventriculography should be performed in patients with previously treated cerebellar medulloblastoma if they should show evidence of recurring symptoms and signs suggestive of a lesion of this type. If this investigation confirmed the presence of obstructive hydrocephalus without obvious recurrence of tumour, operation to relieve the obstruction was indicated in the first instance as opposed to further deep *x*-ray therapy.

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Cold Agglutinins as a Complication of Hypothermia

S. D. K. STRIDE (London) gave a preliminary communication concerning this problem.

Pituitary Destruction by Hypophysectomy and Radioactive Implant for Hormone-dependent Cancer

G. A. GLEADHILL (Belfast) discussed the apparent difficulty of obtaining total abolition of pituitary activity in the treatment of hormone-dependent cancer and described a technique of subfrontal removal reinforced by filling the surgically cleared fossa with a mixture of 10 millicuries of yttrium-90 in 0·8 ml. dental impression wax. The radioactive wax was received as a sterile pellet from Harwell on the day of operation and after being rolled into a thin cylinder was forced into the pituitary fossa by means of a simple syringe designed for the purpose.

Ocular radioactive complications had occurred, two cases having homonymous hemianopia, but no chiasmal damage since a thick piece of muscle had been interposed between wax and chiasma. Four cases of left-sided third nerve paralysis had occurred, due to some wax having been forced into the cavernous sinus through a tear made during curettage. This complication had been avoided by more careful manipulation of the wax when a tear was suspected.

Twenty-one cases had been treated by this method, with three deaths ascribable to operation. Four cases were too recent for hormonal assessment. One case died from an unrelated cause two weeks after operation, in clinical remission but without hormone assay. Of the remaining 13 hormonally-assayed cases, one, which had an unsatisfactory implant, was a failure hormonally and clinically. The other 12 showed absent hormone activity post-operatively. Two of these were, however, clinical failures; they were two cases of local breast disease only, with normal pre-operative radioactive iodine utilization figures of 50%. The other 10 cases are all in clinical remission; they all had blood-borne metastases with pre-operative radioactive iodine uptake figures of 30%.

Some Interesting Tumours Causing Destruction of the Skull Vault

G. K. TUTTON (Preston) presented three cases of extensive destruction of the vault of the skull caused by tumour. Two of these cases turned out to be meningiomas and the third a form of meningeal sarcoma. In all three cases, the history, presentation, and subsequent history showed interesting points. Surgical removal was attempted in two of the cases, one of which ended fatally. In the third case, which had been thought to be a secondary tumour from a mule spinner's cancer of the scrotum, no operation on the head was carried out, the patient dying from the effects of prostatic obstruction.

Case 1.—71-year-old man with a history for two-and-a-half years of a pulsating swelling on the vertex, whose presence had been preceded by a transient attack of left paresis about a year before. When first seen, he had a small swelling just to the right of the midline in the mid-parietal region. His visual acuity was greatly diminished and he had a left hemiparesis. Radiographs of the skull showed an erosion in this area. In view of his age, the poor vision, and the paresis, operation was not advised. Fourteen months later he was seen in a chronic bed. The tumour on the head had increased enormously but his neurological condition had even improved slightly, although he was confined to bed and had a severe left hemiparesis. Under pressure from the patient, his relatives, and being impressed by his comparative well-being, investigations were undertaken. The radiographs and angiograms revealed a grotesque degree of destruction and vascularity. Despite the size of the tumour, the function of the right-sided limbs was normal. He was kept in a continuation hospital for two months and given physiotherapy, encouragement, and good food, so that he could walk around with help. A urea clearance test was 40% normal. After full explanation of the risks involved and under pressure from the patient and relatives to remove the lump from the top of the head, operation was undertaken. Under hypothermia and clamps on both carotids in the neck and the help of hypotension, 780 g. of meningioma were removed. The dura was not opened. The patient died 12 hours later. Necropsy showed extensive bilateral involvement of the falx and longitudinal sinus. Complete removal was probably a technical impossibility.

Case 2.—A 74-year-old man, a mule spinner for 60 years, presented with a painless, non-pulsating lump on the back of the head, the size of a large orange. Neurological examination revealed an attention defect in the left homonymous field, no evidence of raised intracranial pressure but very mild weakness of the left arm. On the scrotum there was a typical mule spinner's cancer without regional nodes. A radiograph of the skull showed gross destruction in the posterior parietal area. No angiogram was performed because needle biopsy of the tumour suggested that it was of the same type as the scrotal cancer, which had been excised. The patient died three months later from the effects of a transurethral resection of the prostate. At necropsy the tumour on the skull was found to be a typical meningioma involving both sides of the falx, almost certainly inoperable.

Case 3.—A woman of 57, in October, 1956, after a fall in the garden developed headache and difficulty in finding the right word. By December, 1956, she had weakness of the right arm and was becoming drowsy and she had evidence of dysphasia. She was admitted to hospital where a tense swelling in the left posterior parietal region was found which on radiology showed a destructive lesion of the bone in this situation. Her condition deteriorated and she became very unresponsive with a right hemiparesis. Needle biopsy secured blood and some pieces of tumour which were reported as being malignant cells, showing mitotic figures. In view of the rapid onset, no operation was advised. The patient was transferred to another hospital and no more heard until six months later when she walked into the Out-patient Clinic. Apparently she had recovered consciousness two weeks after transfer and had then taken her own discharge from hospital and three months later returned to her job as a music teacher. On examination in June, 1957, there was no lump in the parietal region but a bony defect could be palpated. Radiographs of the skull, however, showed an extension of the destructive process. The patient declined further treatment for another two months when she was admitted for an angiogram in August, 1957. At this time the lump had reappeared in the parietal region and also a second lump under the skin had appeared near the external occipital protuberance. Pre-operatively, the tumour was thought to be a meningioma, despite the original biopsy. At operation, the larger of the two tumours was removed, together with a ring of surrounding bone and dura. The tumour was soft, red, and extremely haemorrhagic, and was entirely outside but involving the dura mater. The histological report stated that it was a sarcoma ? of meningeal type but resembling Ewing sarcoma. The causes of the peculiar behaviour of this tumour were discussed.

Whilst no general conclusions could be drawn from these few cases, another case of meningioma was mentioned, which had been present for 18 months in the posterior parietal region and was involving both sides of the falx and actually coming through the bone and underneath the scalp. It was completely removed. If operation is to be at all successful in this type of tumour, then it must be early. Involvement of the longitudinal sinus, the actual size of the tumour, and the technical difficulty of dealing with such a large mass constitute the main surgical difficulties.

Experiments on the Phrenic Nerve of the Seal

R. J. HARRISON (London) discussed the results of various experiments on the phrenic nerve of the seal. He stated that it was known that the common seal (*Phoca vitulina*) exhibited a reflex bradycardia on diving from about 130 beats to 10 beats per minute. It was also known that seals possess certain curious adaptations in their venous system, namely, a caval sphincter rostral to the diaphragm, an hepatic venous sinus and a large extradural intravertebral vein connecting cranial venous sinuses to the renal veins and having many anastomoses with other venous lines (Harrison and Tomlinson, 1956). The striated muscle of the sphincter was supplied by a branch of the right phrenic nerve; the sphincter did not contract when the diaphragm contracted during respiration. It could be shown experimentally that the sphincter was capable of occluding venous return from the abdomen at least in a surfaced animal. Recordings were played to indicate variation in the bradycardia in seals dived to different depths for varying times. It appeared

that the animal exhaled forcibly at the start of a dive. Section of the right phrenic nerve slowed the rate of development of the bradycardia, section of one vagus caused irregular slowing, section of both vagi obliterated the bradycardia. The anatomy of the right phrenic nerve was described, including the number of fibres, their size and distribution and the connexions with the recurrent laryngeal nerve and the sympathetic chain.

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The Surgical Approach to Thoracic Intervertebral Disc Protrusions

A. HULME (Bristol) discussed the operative surgery of thoracic intervertebral disc protrusions. He noted that the results of attempts to remove thoracic intervertebral disc protrusions, using a standard laminectomy approach, were often disappointing. . The hardness and anterior situation of the lesion necessitated harmful manipulation of the cord, which was often already in jeopardy from vascular changes. The operation of simple decompression and division of denticulate ligaments left the primary lesion untreated.

An alternative approach was suggested by the operations of anterolateral decompression and lateral rachotomy in Pott's disease.

Three cases operated on by the antero-lateral approach were described. In each, a hard protrusion was removed with little difficulty and minimal manipulation of the cord. The first case was already paraplegic following a standard laminectomy, and remained so. Both subsequent cases, showing moderate motor and sensory deficit pre-operatively, made virtually complete recoveries.

The operation was conducted with the patient prone. After resection of the medial portions of a rib (including the head and neck) on each side of the affected disc space and enlargement of the intervertebral foramen, the disc protrusion was undercut, using a high-speed surgical burr. The protrusion was depressed into the hollow and withdrawn, with little disturbance to the cord.

An accurate pre-operative diagnosis was essential. Characteristic radiological changes in the spine, especially calcification in the disc spaces or posterior osteophytes, were often helpful. Careful myelography was essential to determine the exact level of the lesion and to confirm its anterior situation.

The E.E.G. Investigation of a Case of Epilepsy

S. L. LAST (London) discussed one case and showed extracts of the electroencephalograms and electrocorticograms obtained and demonstrated the type of intracranial electrodes used. The case was one of a man, aged 37, who for 10 years had attacks of psychomotor epilepsy. These had become very frequent and at times occurred every 10 minutes and he usually had at least four a day. Lately the attacks were preceded by joyless laughter. Eleven records were taken before the operation. These included activation by over-breathing, " seconal ", and chlorpromazine. Five of the records were derived from implanted electrodes; some of these were lying on the surface of the brain, others were inserted in the substance. The findings were variable and showed abnormality to predominate sometimes on the right and sometimes on the left side. However, the most constant finding was of a high-voltage spike originating near the orbital surface of the frontal lobe. This was further confirmed by electrocorticography during a right-sided frontal craniotomy. An area containing the spike focus was excised. A fortnight later the E.E.G. still contained much abnormality on the right side.

A month after the operation the patient returned to work. Six-and-a-half months after the operation he had remained at work. He had had no more attacks and his record had become almost completely normal.

Radioactive Isotopes in Neurology

H. J. CROW (London) presented his views on the use and the value of radioactive isotopes in neurology. He considered that some confusion had resulted from the misinterpretation of results in experiments with radioactive isotopes. He agreed with Dr. R. Silverstone who had argued that much of the current confusion in thought about cerebrospinal fluid production and absorption arose from the failure to appreciate the difference between the flow of fluid and the exchange of ions across a semi-permeable membrane.

From his observations he concluded that at present the only practical use of a radioactive isotope in hydrocephalus was to give an index of cerebrospinal fluid movement, which might enable the effect of operation to be tested. The patient must be used as his own control. A simple technique was described for testing the patency of tubes in subarachno-peritoneostomy, subarachno-ureterostomy, and ventriculo-cisternostomy.

An experiment, performed on dogs, was described which was claimed to demonstrate the following points:

1. There was a blood-brain barrier to sodium, 20 hours being required for complete equilibrium.

2. In respect of sodium at least, cerebrospinal fluid behaved like an integral part of the extracellular fluid of adjacent nervous tissue.

3. The rate of uptake of sodium from the plasma into the central nervous system varied from region to region.

The explanation, which it was claimed had been demonstrated, was as follows. All regions of the central nervous system received sodium through their capillaries at the same rate. Cerebrospinal fluid flowing from the ventricles delivered extra sodium to the central nervous system, the proximal regions receiving their cerebrospinal fluid moiety of sodium before the distal regions.

The Surgical Treatment of Aneurysms in the Posterior Fossa

VALENTINE LOGUE (London) discussed the surgical treatment of posterior fossa aneurysms and presented the clinical and operative features of six personal cases. Consideration was restricted to aneurysms lying below the level of the tentorium on the vertebral and basilar arteries and their branches up to the bifurcation of the basilar artery. All the cases were examples of ruptured

saccular aneurysms with subarachnoid haemorrhage. Previous reports on these aneurysms had suggested that they were untreatable and had influenced neurosurgeons against making further investigations after negative carotid angiograms in cases of subarachnoid haemorrhage. Certain features, however, made their treatment somewhat easier than that of supratentorial aneurysms. They lay free in the subarachnoid space so that little brain retraction was needed to expose them, both vertebral arteries were easily visible in a posterior fossa approach, and the whole length of the basilar artery could be exposed through a transtentorial approach, and finally, the dual vertebral supply made occlusion of one artery a possibility. Clinical features were not considered in detail but experience had shown that some cases evidenced symptoms and signs pointing to a posterior fossa location whilst others could only be diagnosed by vertebral angiography, usually after a negative carotid angiogram.

Case 1 (*Superior Cerebellar Artery*).—A woman of 56 had suffered from migraine all her life and had had two attacks of suboccipital and right aural pain associated with transient unconsciousness. Signs: reduced corneal reflex on the right and bilateral extensor plantar responses. Carotid angiography was normal. Two further coma-producing haemorrhages occurred leaving her with fifth sensory impairment, a sixth nerve paresis, and hearing loss on the right side. Vertebral angiography showed an aneurysm on the right superior cerebellar artery. Operation: transtentorial approach and removal of aneurysm after clipping the artery on either side; section of the fifth nerve was necessary. Six years later leading a normal life and fifth nerve anaesthesia and slight facial contracture the only residual signs.

Case 2 (*Basilar Artery*).—A woman of 49 had one subarachnoid haemorrhage. A carotid angiogram was normal. A vertebral angiogram showed an aneurysm at the upper end of the basilar artery, its apex giving rise to both posterior cerebral and superior cerebellar arteries. Operation by a subtemporal route confirmed this situation and the aneurysm was packed around with muscle. The patient is now leading a normal life without residual signs.

Case 3 (*Posterior Inferior Cerebellar Artery*).—A man of 25 had four subarachnoid haemorrhages. Normal carotid angiogram. Right vertebral angiography showed a normal right vertebral but poor filling of the basilar artery. A left vertebral angiogram showed the aneurysm on the left posterior inferior cerebellar. Operation: posterior fossa approach and a large aneurysm clipped at its base, leaving the derivative vessel intact and sac removed. Recovery complicated by a tentorial block and hydrocephalus requiring anterior third ventriculostomy. A year later had returned to light work and the only residual signs were nystagmoid jerks and difficulty in balancing on one leg.

Case 4 (*Vertebral Artery*).—A woman of 50 had one subarachnoid haemorrhage. Carotid angiogram was normal. Vertebral angiography showed a saccular aneurysm of the left vertebral arising by a neck. Operation: base of aneurysm occluded by a clip. Two and a half months later was doing normal housework and her only residual sign was a spinal accessory weakness.

Case 5 (*Vertebral Artery*).—A woman of 47 had three attacks of subarachnoid haemorrhage with greatly reduced vision from retinal haemorrhages. Normal carotid angiogram, but a vertebral angiogram showed an aneurysm of the right vertebral artery. At operation the aneurysm was found to be a saccular dilatation of the vertebral artery. The vertebral artery was occluded proximally with a clip. She developed ischaemic signs and recovered slowly from these. Nine months after operation was doing housework, vision remained very poor, there was a right Horner's syndrome, and considerable ataxy of gait.

Case 6 (*Vertebral Artery*).—A man of 55 had two subarachnoid haemorrhages. Carotid angiograms were normal. A vertebral angiogram showed an aneurysm on the left vertebral artery and spasm of the basilar. The aneurysm was found at operation to be a saccular dilatation of the vertebral artery and a proximal clip was applied. He developed mild ischaemic signs but made a good recovery. Fourteen months after operation he was doing light work and the residual signs were nystagmus and some sensory reduction in the right lower leg.

It was stressed that contrary to reported views proximal clipping of a vertebral artery reversed the blood flow in the vessel and profoundly reduced the pressure in it. The immediate decrease in the size of the sac and pulsation and the later development of ischaemic signs was sufficient proof of this. The freedom from bleeds following operation was further clinical proof of its value. It was further emphasized that a careful search for evidence of a posterior fossa location would avoid the necessity for carotid angiography and that vertebral angiography would be carried out as a routine when carotid angiograms were normal in cases of subarachnoid bleeding.

Footballer's Amnesia

JOHN POTTER (Manchester) discussed the question of a particular type of amnesia encountered in football injuries. Cases of mild head injury where the blow was remembered and yet post-traumatic amnesia (P.T.A.) followed were unusual. Russell and Nathan (1946) suggested that delayed P.T.A. indicated "vascular complications"; in accidental head injuries its incidence was 2·5% but in gunshot wounds 14%.

In one year at the Radcliffe Infirmary, Oxford, almost all of 522 patients with head injuries were questioned about their amnesia. Ten had no retrograde amnesia (R.A.) but P.T.A. started about a second to 15 minutes after the injury and lasted from a few minutes to about two hours. This general incidence of about 2% compared with Russell and Nathan's 2·5%. Almost all the remaining cases had amnesia and this was of the conventional pattern of R.A. and P.T.A.

Of the 522 cases, 19 were football injuries and six of these showed P.T.A. only, a remarkable incidence of 30%.

None of the cases with P.T.A. only appeared to have had a fit, but syncope may have occurred in three. Subarachnoid and subdural bleeding was present in another. Only two cases showed any resemblance to Denny Brown's (1941) cases of "delayed collapse".

Vascular or vasomotor complications were the most satisfactory explanation of such a delayed phenomenon and it was interesting to recall the experimental findings of Denny Brown and Russell (1941) concerning stimulation of the vaso-glossopharyngeal system which was

observed to occur even in sub-concussive injuries. In the cases under consideration it was possible that we were observing vascular effects which in more ordinary concussion were concealed by overlapping of the primary neuronal disintegration.

Why should football injuries provide such a disproportion of these atypical cases ? Trauma as focal and with as low a velocity as a kick should occur in a general run of some 500 other accidents to the head. Many injuries at football were received during a spell of marked physical exertion and it might be that these delayed effects were the result of a sub-concussive blow on the brain during a physiological state of the body that was not operative when most head injuries were sustained.

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Arterial Spasm in Subarachnoid Haemorrhage: Mechanical Considerations

R. J. Johnson, J. M. Potter, and R. G. Reid (Manchester) mentioned briefly the various factors which had been shown to influence the calibre of the cerebral arteries in experimental animals. Most important were (*a*) changes in systemic blood pressure, temperature, and CO_2 tension, (*b*) accumulation of metabolites, and (*c*) vasoconstrictor and vasodilator nerves. The changes in calibre produced were for the most part of minor degree, the gross vasoconstriction of spasm being produced solely by local trauma to the vessel wall.

There were, however, three pitfalls in the arteriographic diagnosis of spasm; first the vessels might be narrowed congenitally or by reason of arteriosclerosis; secondly, even if the diagnosis of spasm was only accepted (as should be the case) if the vessel was demonstrated both in its normal and constricted state, temporary narrowing might be produced by stretch of a vessel round an intracerebral clot or a large aneurysm; and thirdly, the appearance of narrowing might be produced by variations in blood flow. This was encountered in (i) nonfilling of the anterior cerebral artery, often attributed to spasm as a result of needling the carotid, or as a result of spontaneous dissection of an atheromatous plaque but which might be produced by restricting the blood flow through the injected carotid, when both anterior cerebrals filled from the opposite side, and (ii) streaming of the contrast medium which closely simulated spasm and which might be demonstrated by trickle angiograms.

True spasm of the cerebral arteries had been produced during neurosurgical operations so one need have no worry about the propriety of applying to the human brain this finding in experimental animals. It was probably seen best and in its purest form in the subarachnoid loops of the posterior inferior cerebellar artery which in some instances might be driven into spasm by merely twanging one of the supporting arachnoid bands. The vessel narrowed and also shortened and within a minute or less returned to normal. It was doubtful if this change produced any serious reduction in blood flow under physiological conditions: the trauma required was slight and certainly no more than might occur as a result of a head injury or the outpouring of blood into the subarachnoid space as a result of leakage from an aneurysm or angioma. It might also be observed at operation that vessels of the calibre of the middle and anterior cerebral arteries became smaller as the blood pressure was lowered by hypotensive drugs and a little manipulation at this stage encouraged the vessel wall to contract down, although it was difficult to be sure what degree of narrowing under such conditions constituted spasm.

Spasm was a major problem in the management of intracranial bleeding, for it might be a concomitant of pure subarachnoid haemorrhage (unassociated with any intracerebral clot) from a small aneurysm or angioma, and yet cause severe morbidity and not infrequently death. It only occurred when there had been bleeding and usually only in the presence of severe bleeding and it had several features: 1. It was confined to the intradural vessels. 2. It might be proximal or distal to the aneurysm and might be on the opposite side. 3. It was patchy and irregular and the length of involved segments varied considerably. 4. It was essentially proximal, always near the circle of Willis, frequently involved the carotid syphon and yet distal vessels were normal. 5. It caused slowing of the cerebral circulation. 6. The narrowing might persist for weeks, a feature which suggested structural changes in the vessel wall.

They offered evidence that " spasm " was produced and maintained by the mechanical effects of the subarachnoid haemorrhage. Blood poured out from a " subarachnoid " aneurysm would fill the basal cisterns and travel along the subarachnoid spaces surrounding the main branches of the circle of Willis. Susceptible arteries would be thrown into spasm by physical stretch or by pull on attached arachnoid bands. Rapid return to normal failed to take place either because of intrinsic damage to the vessel wall or because of the surrounding blood clot. An added factor was the distortion and rotation that might occur at the carotid bifurcation by twist of the aneurysm as it bled; this lowered the local blood pressure and reduced the flow, accentuating the effect of the narrowing.

Recovery occurred at an interval which varied with the pathology, *i.e.* (1) the nature and extent of damage to the vessel wall, (2) the rate of dispersal of surrounding blood clot, (3) return to normal of a kinked main vessel, and (4) the final dissolution of arachnoidal adhesions formed around the vessel in response to the clot.

Carotid kinking and arterial " spasm " due to subarachnoid blood clot were demonstrated at operation and at necropsy, the " spasm " remaining unchanged in the post-mortem angiogram.

They suggested finally that a comparatively small amount of subarachnoid blood clot could maintain narrowing of main vessels and cause serious ischaemia and that this might be an indication for early surgery in an attempt to free the main vessels, quite apart from treatment of the aneurysm itself.

Intrathecal Phenol for Intractable Pain: Safety and Dangers of the Method

P. Nathan (London).

Intrathecal Phenol for Intractable Pain: Histological Findings

M. C. SMITH (London).

The Effects of Anterior Choroidal Artery Division

P. R. R. CLARKE and B. E. TOMLINSON (Newcastle-upon-Tyne) discussed the effects of anterior choroidal artery occlusion. The importance of the functional anatomy of the anterior choroidal artery in neurosurgery was mentioned in relation to the surgery of Parkinsonism and of aneurysms of the circle of Willis. The discrepancy between the older views regarding its distribution (Abbie, 1934), and that of Cooper (1956), who had stated that the globus pallidus was the only area irrigated by the artery to have virtually no other constant source of blood, was discussed.

A case was described of a young man of 24, who underwent division of the left anterior choroidal artery in an attempt to improve his torsion spasm. In the immediate post-operative period there was a right spastic hemiplegia with weakness of the left superior oblique and inferior rectus muscles and right hemi-anaesthesia to light touch. Death from an unrelated cause took place seven weeks after operation and a detailed examination was made of the brain. An extensive area of infarction was found involving the upper portion of the middle third and some of the posterior third of the posterior limb of the internal capsule, the medial part of the globus pallidus and the neighbouring portion of the internal capsule, the ansa lenticularis, much of the amygdaloid nucleus, and some of the tail of the caudate nucleus and of the uncus.

It was stressed that the vascular system in this patient appeared entirely normal and that the anterior choroidal artery was the only one to have been divided.

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Diagnostic Cortical Biopsy: A Histological and Chemical Study

W. BLACKWOOD and J. N. CUMINGS (London)

The Significance of Lead Poisoning in Neurological Surgery

W. J. ATKINSON (London) described a case of lead encephalitis which had presented as a difficult diagnostic problem in the Neurosurgical Department of the London Hospital. The patient was a three-year-old child who had had 24 hours of malaise and projectile vomiting which was followed by rapid loss of consciousness. Anaemia had been diagnosed and investigated a year previously at a local hospital.

On admission he was unresponsive to painful stimuli, had Cheyne-Stokes respiration, inactive dilated pupils, and equivocal plantar responses. There was a recent perforation of the right tympanum but no evidence of chronic ear disease. Bifrontal and right temporal burr-holes revealed no collection of fluid; the lateral ventricles could not be tapped. By the following day he had improved considerably and had recovered completely in four days. Ventriculography revealed lateral ventricles which were of maximum size for a normal child. The E.E.G. records resembled superficially those of subacute vascular encephalopathy and virus encephalitis but returned to normal within a week. Erythrocytes showed punctate basophilia, the long bone radiographs showed lead lines, and the urine contained coproporphyrin and excessive concentrations of lead. He continued to remain well and received courses of calcium vasenate.

In America, lead poisoning usually presented in children with vomiting, convulsions, and papilloedema. Bucy and Buchanan (1935) and others had advocated and practised cranial decompression for their cases. In the acute case entering a neurosurgical ward the appearance of lead lines in the long bones radiographically was the quickest way to a diagnosis which could be confirmed later by finding coproporphyrins and excessive lead in the urine.

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Symptoms of Cerebral Abscess since the Introduction of Antibiotics

C. J. EARL and M. YEALLAND (London)

BOOK REVIEWS

Physiology of the Nervous System. By E. Geoffrey Walsh. (Pp. 563. 50*s*.) London: Longmans Green. 1957.

Neurophysiology has advanced rapidly in the past two decades, and these advances have often had direct clinical relevance. This new and up-to-date textbook will thus be equally welcome to physiology students and to clinical neurologists. The author is well aware of the clinical implications of his subject matter and draws on clinical material to illustrate his argument where appropriate. A separate chapter on the applied physiology of pain by Dr. John Marshall adds to its value. The book is written in a pleasant and lucid style and is happily free from "scientific journalese". It gives a refreshing impression of analysing the nervous system in the activities of everyday life. The mention in the text of a main reference source to certain subjects is useful; in addition, a full list of references to "classical" and modern papers is given at the end.

Modern Trends in Neurology (Second Series). Edited by Denis Williams. (Pp. xi + 350 + index. 72*s*. 6*d*.) London: Butterworth & Co. 1957.

The subject matter of clinical neurology has a more direct link with its basic sciences than have some other branches of medicine, and advances in these sciences therefore call for rapid integration with clinical work. This makes it more difficult to keep text-books up to date and enhances the value of such books as this which review modern trends. It also allows editors and contributors to be selective and to emphasize what they consider currently important aspects of their subject. The present volume fulfils both these functions admirably. Its 24 chapters deal with physiological, biochemical, and cytochemical problems as well as those of pathogenesis and more purely clinical medicine. Professor Lumsden's description of the dynamics of myelin maintenance and the activities of oligodendrocytes are particularly interesting, both in their own right and for their relevance to the problems of demyelinating diseases, sensitization phenomena in the nervous system, and virus invasion, all of which are discussed by various authors. Dr. Nathan's succinct review of modern knowledge of the inter-connexions of thalamus, hypothalamus, and cortex is useful. Professor Meyer does much to put into proper perspective recent work on local lesions in the causation of temporal lobe epilepsies. The book discusses matters of interest to all neurologists, neurosurgeons, and psychiatrists.

Peripheral Nerve Regeneration: A Follow-up Study of 3656 World War II Injuries. Edited by Barnes Woodhall, and Gilbert W. Beebe. (Pp. xvii + 671; 286 tables, 60 plates.) Washington, D.C.: Veterans Administration. 1956.

This book is a fine monument to American neurosurgeons who dealt with nerve injuries during the Second World War. The records were kept in great detail, and important practical problems of treatment and prognosis were solved. A statistical analysis of the functional disability and the effect on employment is of special value, and gives the surgeon a good idea of what should be expected of his patient.

Although this work contains so much of great value to the surgeon it is disappointing to find so little reference to the all-important handling of these cases as regards physiotherapy, restriction of free use of the limb, *etc.* Apparently these patients were kept in hospital for very long periods (over 85% for over 400 days) and it is difficult to see what good these long periods of hospital treatment could do. Certainly there is no attempt to justify such a very extreme policy of close supervision.

There is also little attempt to study many of the physiological problems regarding regenerating nerves such as the occurrence of mass movement, the rate of nerve conduction or the physical proportion of denervated muscle.

However, in spite of these shortcomings, this work should be read by those who deal with nerve injuries.

Die vaskulären Erkrankungen im Gebiet der Arteria vertebralis und Arteria basialis. By H. Krayenbühl and M. G. Yaşargil. (Pp. viii + 170; 125 figures on 205 plates. D.M. 69.30.) Stuttgart: Georg Thieme Verlag. 1957.

This monograph from Zurich is an outstanding contribution to a subject which has assumed increasing importance in recent years, ever since vertebral arteriography has become widely used. The sections on anatomical variations, clinical syndromes, aneurysms, and vascular malformations are of special interest. Neurologists, neurosurgeons, and radiologists should have this book available for reference.

Collection Testut. Precis de Neurologie, 6th ed., entirely revised. By L. Rimbaud, in collaboration with P. Passouant and Cl. Gros. (Pp. xiv + 1,186; 331 figures. Fr. frs. 8,700.-.) Paris: G. Doin. 1957.

This is a text-book of neurology rather than a synopsis. The text has been revised for this sixth edition and new material added, particularly in the sections on the acute

infections of the nervous system. The text follows orthodox lines with short accounts of anatomy and physiology and excellent detailed descriptions of neurological disorders. There are a number of illustrations, many of them reproduced from other text-books, but the reproductions of radiographs are poor. The names of many authors are given in the text after various statements but no references are given so detracting from the value of the book.

Psychosomatic Medicine, 3rd ed.: **A Clinical Study of Psychophysiologic Reactions.** By E. Weiss and O. S. English. (Pp. xix + 557; 10 figures. 73*s.* 6*d.*) London: W. B. Saunders. 1957.

This is the third edition of a book which has won an established place in neuropsychiatry. It has been said that psychological medicine is " the other half of medicine " (and some may add the more important half). This book may be viewed as an illustration of this theme. All disease is to some extent " psychosomatic ": but in some diseases manifested in physical signs the psychological precipitants are more obtrusive than in others. Asthma is often cited as an example, and a variety of gastro-intestinal upsets—mucous colitis, nervous diarrhoea, and some forms of dyspepsia—are of the same group. These first earned the name " psychosomatic ", but they provided a jumping-off place for a much wider interpretation of the ways in which psychological factors—in practice mainly emotional ones—influenced physiological mechanisms to produce symptoms. It is this wider and more fundamental sense of psychosomatic medicine which is admirably dealt with in this book. The first four chapters describe the basic psychological mechanisms involved and their ways of influencing physiology. Thereafter, chapters are devoted to the application of these principles in disease of each of the main bodily systems. Illustrative case histories form a valuable part of the text. There is perhaps a slight tendency to overlook the two-way nature of psychosomatics and to concentrate on the psychogenesis of physical states to the exclusion of the physical factors which may start, or more often aggravate, psychological symptoms. This may be inevitable after a century or more of exclusive emphasis on the physical origin of disease. It is in any case less marked in this than in many books on this subject. Neurologists and psychiatrists can hardly fail to find this book interesting: nor, unless they are working intensively in this field themselves, can they fail to be informed by it.

A Text-book of Psychiatry, 8th ed. By D. Henderson and R. D. Gillespie. (Pp. xii + 746. 35*s.*) London: Oxford University Press. 1956.

This text-book has now passed through eight editions and has been in very active circulation for 30 years. When it first appeared, psychiatry was feeling the impact of Freudian psychopathology and its derivatives: since then the growing point of psychiatric research has changed, and the organic substrate of mental disease is occupying increasing interest. It is a tribute to this book, and especially to the Meyerian psychobiological psychiatry it represents, that it has been able to some extent to encompass this change of psychiatric emphasis within its original framework. To a psychiatrist of the 1920s visiting either an active university centre or an outlying mental hospital today the striking change would undoubtedly be in the development of physical methods of treatment. Psychosurgery, electroplexy, insulin, and a large number of tranquillizing, euphoriant, and even hallucinatory drugs would be novel or greatly expanded methods of treatment. But these are only the outward and visible signs of a more widespread interest in the fundamental biochemistry and biophysics of the cells of the body, and especially the brain, as fundamental factors in mental disease. This is what is giving psychiatry its " new look ", and it is inevitable to ask how any modern psychiatric text-book presents this aspect of the subject. The eighth edition of the book is certainly aware of the changing outlook, mentions it where appropriate in discussion of aetiology and even nosology, and even refers to some of the recent literature. However, there is a slight impression that it is at present grafted on to the older text rather than an integral part of it. There is nothing in these recent trends that is foreign to Meyer's widely based biological approach, and doubtless further editions of the book and the advances of this aspect of psychiatry will give the authors an opportunity to emphasize the wider implications of this approach. Meantime, while fundamental causes elude us, descriptive psychiatry will remain essential. As a text-book of descriptive psychiatry this work continues to be a most excellent introduction and deserves its place as the leading short text-book of British psychiatry.

Practical Clinical Psychiatry, 8th ed. By Jack R. Ewalt, Edward A. Strecker, and Franklin G. Ebaugh. (Pp. xiv + 457. 60*s.*) London: McGraw Hill. 1957.

The eighth edition of this American text-book has been very thoroughly revised, so much so that it is virtually a new book. It has been reduced by about 50 pages from the previous edition, largely by the exclusion of case histories, but is a thicker book, being printed on much poorer paper.

One can summarize by saying that this book is a fairly orthodox presentation of American dynamic psychiatry. This will be sufficient indication for many psychiatrists of the book's merits and demerits: for others, one can say that the emphasis throughout is on psychodynamic theories rather than facts. For example, the psychopathology of endogenous depression receives six pages but Kallman's figures are dismissed in a paragraph. This is reasonable only if one agrees with the authors that " increasing evidence accumulates to support this belief that psychologic causes of this disorder are the predominant ones ".

The emphasis in the discussion on psychodynamics leads to incongruities. In the treatment of the affective

disorders one has the impression that psychotherapy is the treatment of choice, for E.C.T. receives scant mention. It comes somewhat as a surprise, therefore, to read further on in the same chapter that the authors feel that they can dispense with instructions about the maintenance of the physical health of depressed patients because "the advent of shock therapy . . . makes patients' symptoms evolve so rapidly . . . "

The literature surveyed is almost exclusively American: on the subject of post-traumatic syndromes, for instance, one reads with astonishment that "according to verbal reports from the Office of Scientific Research and Development", the duration of the period of unconsciousness following head injury is the best guide to the severity of the post-traumatic changes. In these days of fast travel, it should not take 23 years for Ritchie Russell's work to cross the Atlantic.

All in all, a very uneven book, likely to confuse rather than educate.

The Clinical Examination of Patients with Organic Cerebral Disease. By R. Klein and W. Mayer-Gross. (Pp. xiii + 96; 9 figures. 15*s*.) London: Cassell. 1957.

The examination of the patient with organic cerebral disease often falls between the two stools of psychiatry and neurology. While the neurologist is interested in dysphasia and its ramifications, he is often uninterested in or ignorant of confusional states and their content. The psychiatrist on the other hand may recognize clearly enough the confusional state and assign a correct psychogenesis to some of its contents while missing the element of agnosia or apraxia that is playing a part in the clinical picture. It is just such a borderland that this small book deals with. Its systematic approach will be useful to both neurologists and psychiatrists who do not meet a great many of such cases, although those who see many may feel that many aspects really require rather fuller treatment than is here afforded. It can be recommended as an introduction to the subject, particularly to students for the Diploma of Psychological Medicine.

Pneumoencephalography. By E. Graeme Robertson. (Pp. xxi + 482; 34 plates, 209 figures. 110*s*.) Oxford: Blackwell Scientific Publications; Springfield, Illinois: Charles C. Thomas. 1957.

This book is the third to be written on air encephalography by this author since he became interested in the subject over 20 years ago. He is well known as one of the originators of modern techniques of air encephalography which have greatly increased its safety and decreased its discomforts. Other workers have tended to simplify the technique and have adapted it to investigate patients with raised intracranial pressure, a practice which the author himself deplores.

This volume contains clear descriptions of the author's technique of air encephalography, of the normal brain anatomy disclosed by air injections, and of his theories on the mechanism of ventricular filling. Much of those sections appeared in previous volumes, but their reproduction is welcome because copies of the author's first book ("Encephalography") have been unobtainable in this country for several years. This present book also contains excellent descriptions of the abnormal conditions likely to be encountered, including injuries, vascular disease, congenital lesions, and diseases in childhood. The section on space-occupying lesions shows the reasons for the various abnormal signs produced by masses in different situations, rather than giving mere lists of changes. The author pays particular attention to information obtained from deformity of the basal cisterns in all his descriptions. There is also a very useful chapter on the causes of failure to obtain air-filling of the ventricles and on the remedies to be applied.

The book is well printed and is profusely illustrated with clearly coloured plates and excellent radiographs. It should become a standard text-book on the subject of air encephalography and should appeal to all those who are interested in neuroradiology.

Tranquillizing Drugs. Arranged and edited by Harold E. Himwich. (Pp. viii + 205; 32 figures.) London: Bailey Bros. & Swinfen. 1957.

This small volume represents the outcome of a symposium on tranquillizing drugs arranged jointly by the American Psychiatric Association and the American Physiological Society. Experimental investigations in animals of some of the electrophysiological effects are reported. Clinical aspects of the drugs, especially in the treatment of psychotic states, are also described, and some problems of dosage and side-effects are mentioned. The book will be of interest to psychiatrists and neurologists wishing to know something of applied biochemistry in this field.

Correction

In this paper, "The Entry of Radiosodium and of Bromide into Human Cerebrospinal Fluid" (*J. Neurol. Neurosurg. Psychiat.*, **20**, 79) by R. B. Bourdillon, M. Fischer-Williams, Honor V. Smith, and K. B. Taylor, Figs. 1 and 4 have been transposed, though the legends are in the correct positions. Thus the legend under the present Fig. 1 explains the graph shown as Fig. 4 and *vice versa*. In addition, the legend to Fig. 1 should read: Effects of age in patients with *no* abnormal physical signs.

Societa' Italiana di Neuro Chirurgia

The Societa' Italiana di Neuro Chirurgia will hold its ninth congress in Florence on April 24 and 25, 1958. Two subjects will be discussed:—

(1) Cerebral abscesses and suppurative encephalitis

(2) Cervical discal herniations and cervical spondylosis

Further information may be obtained from the Secretary (Dr. Giulio Morello, Via Celoria 11, Milan, Italy).

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THE NEUROPATHY OF MULTIPLE MYELOMA*

BY

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Much has been written about disorders of nervous function due to tumours of the plasma cell type (plasmacytoma and multiple myeloma). Detailed discussions of this subject and reviews of the literature are to be found in the monograph of Snapper, Turner, and Moscovitz (1953), and in the comprehensive articles of Geschickter and Copeland (1928), Davison and Balser (1937), Shenkin, Horn, and Grant (1945), and Bayrd and Heck (1947). These writings make repeated reference to several syndromes resulting from compression of neural structures by masses of tumour tissue. By far the best known of these is " myelomatous paraplegia " due to compression of the spinal cord by extradural deposits of myeloma and occasionally by a collapsed vertebra. Similarly, nerve roots and peripheral nerves may be compressed by myelomatous tissue extending from contiguous bone. Cranial nerve palsies may result from myelomatous compression at their foramens of exit at the base of the skull and less commonly there may be neoplastic invasion of intracranial or intraorbital structures. These orbital and intracranial complications of multiple myeloma have recently been reviewed by Clarke (1953, 1954). Herpes zoster is a rare complication of multiple myeloma (Anders and Boston, 1903; von Bomhard, 1914; Wallgren, 1920) and, most recently, median neuritis due to amyloid deposition in the carpal ligament has been described† (Grokoest and Demartini, 1954).

The topic to which we invite attention is a curious and little known affection of peripheral nerves which is only obscurely related to multiple myeloma, for the disease, unlike the aforementioned neurological syndromes, does not in any way depend on compression of nervous structures by tumour tissue. The literature dealing with this particular neurological complication is meagre and in only one of the reported cases to date can the pathological description be considered adequate (Scheinker, 1938). We therefore feel justified in presenting the clinical findings in five cases which have come under observation in recent years. In three of these post-mortem examinations were performed and in one other appropriate biopsy material was procured.

Review of the Literature

Although the literature on multiple myeloma contains a considerable number of references to peripheral nerve involvement, very few of the reported cases can be accepted as authentic examples of polyneuropathy. This is particularly true in the writings which deal primarily with other than the neurological aspects of multiple myeloma. Here the occurrence of neuropathy is merely mentioned, with little or no description of the neurological signs. Falling into this category are Case 3 of White and Tillinghast (1950) and Cases 6, 8, 10, and 14 of Madonick and Solomon (1953). Snapper *et al.* (1953) recognize a form of a peripheral neuritis in multiple myeloma in which no direct involvement of nerves or nerve roots could be demonstrated. They state that four of their cases developed a " glove-and-stocking " type of peripheral neuritis but provide no further clinical or pathological data to support their statement. The cases mentioned by Levison (1933) and Levison and Møller (1924) and Case 3 of Lawrence and Rosenthal (1949) may have been instances of polyneuropathy with multiple myeloma, but again the clinical and pathological data are so scant that one is reluctant to accept the diagnosis of polyneuropathy. The same criticism applies, in general, to the cases of Neel (1931). However, one of his cases did show, on pathological examination, a disappearance of the myelin sheaths of the peripheral nerves of the lower extremities and to a lesser degree of the upper extremities. Unfortunately, there was also an irregular tumour mass involving the dura, so that it cannot be taken to

*The pathological studies were aided in part by a research grant (M-767) from the National Institute of Mental Health, United States Public Health Service.

†We have also seen a 44-year-old man who developed a bilateral carpal tunnel syndrome in the course of multiple myeloma. The symptoms responded to division of the carpal ligaments, which contained amorphous masses suggestive of amyloid.

represent a pure example of the syndrome under discussion.

Kurnick and Yohalem (1948), Estes and Millikan (1954), and Clarke (1956) have written specifically on the association of peripheral neuropathy and multiple myeloma and have claimed that the neurological changes were not due to direct involvement of nerve tissue. Their evidence was purely clinical, however, for they had no opportunity to verify this impression pathologically. Kurnick and Yohalem described three patients. In their first patient, the signs of neuropathy were practically limited to the right hand. Their second patient showed a symmetrical sensorimotor neuropathy affecting the feet and hands. The authors assumed that there was no invasion or compression of nervous structures by myelomatous tissue in these two patients, despite lack of pathological confirmation and the focal nature of the neuropathy in their first patient. The third patient had signs of a mild neuropathy and nocturnal pain was a prominent symptom. This patient was also diabetic, a state which may have accounted for the symptoms. At necropsy the peripheral nerves were not examined.

Estes and Millikan (1954) have reported the case of a 43-year-old woman whose chief complaints had been extreme weakness and pain in the legs. These symptoms were progressive and were followed by constrictive sensations around the chest. There was weakness of the proximal musculature of the legs and absent knee jerks, as well as a loss of superficial sensation below the level of the second thoracic dermatome. Although there was no clinical evidence of an epidural tumour, an operation or post-mortem confirmation of this fact was not obtained; the discrete sensory level on the trunk would be an unusual finding in our experience in a case of polyneuritis and radiculitis.

The case reported by Clarke (1956) is an undoubted example of multiple myeloma, which, though unverified pathologically, satisfies the clinical criteria for the diagnosis of polyneuropathy. Clarke also cites the case of Berlin (1946) and a case report from the Massachusetts General Hospital as examples of myelomatous neuropathy. Berlin's case is not entirely acceptable. The patient was a severe hypertensive (blood pressure 215/115 mm. Hg) who showed ataxia, foot drop, and absent knee and ankle jerks, but no sensory signs. His symptoms were said to regress with the administration of a vasodilator drug but his ultimate fate was not determined. The Massachusetts General Hospital case was suggestive of polyneuropathy on clinical grounds but post-mortem examination showed no abnormality of the peripheral nerves. We have reviewed the pathological material in this case; it represents an instance of amyloidosis complicating multiple myeloma and will be commented on further in the discussion.

The most convincing descriptions of the neuropathy under discussion are those of Davison and Balser (1937) and of Scheinker (1938). One of the patients with multiple myeloma reported by the former authors was a 49-year-old woman, who had had a progressive history over two years of parasthesiae, weakness, and wasting of the hands. Post-mortem examination disclosed no myelomatous invasion of the brachial plexuses, although there was, on microscopic examination, demyelination and degeneration of the axis cylinders to be seen in these nerves. The spinal cord, spinal ganglia, and radicular nerves were not examined.

Scheinker (1938) reported a well documented case of a 39-year-old man with a progressive neuropathy of two years' duration. The patient had had signs of both sensory and motor involvement beginning in the legs and later affecting the arms, and there was also a raised cerebrospinal fluid protein level. Necropsy disclosed a solitary plasmacytoma of the sternum. The nervous system was not directly involved by tumour, but nevertheless there was a patchy degeneration of myelin and axis cylinders in the roots and peripheral nerves, including the phrenic nerve. Moreover, the spinal cord sections, stained by the Pal-Weigert and Spielmeyer methods, showed at every level a slight pallor in the posterior columns, indicating a loss of medullated fibres. There was also, with Nissl stains, evidence of cellular destruction in the grey matter. Because of the proliferation and thickening of the perineural connective tissue, Scheinker termed this neuropathy " perineuritis interstitialis scleroticans ".

The literature on myelomatous neuropathy contains a number of reports of other neurological syndromes in which no contiguous or invasive myelomatous lesions of the nervous system were evident. Frequently quoted in this connexion are the reports of Senator (1899) and of Nonne (1921), who, lacking anatomical proof that tumour had impinged on nerves or spinal cord, ascribed the neurological symptoms to a toxic state. The data in these reports are quite incomplete, and one cannot be certain that the patient suffered only from myeloma and that pathologically, tumour had not involved the nervous system. In the case of Kreuzer (1926), the author states that the spinal cord was in no way compressed by the tumour; nevertheless, there was an epidural plasma cell tumour extending from the fourth to seven thoracic segments and extravasation of blood in the underlying cord. The case of Lindeboom and Mulder (1941) is the most convincing of this group. They described a patient with multiple myeloma who rapidly developed an asymmetrical paraplegia

with a sensory level on the trunk. Pathologically there was no evidence of compression of the spinal cord by myeloma, but there was degeneration, evident with myelin stains, of all the funiculi of the cord.

Case Reports

Case 1.—Y. S., a Portuguese 45-year-old mother of seven, was first admitted to the Massachusetts General Hospital on June 26, 1953. Her illness had begun one year previously with mild pain in the lower back and in the right hip, often radiating along the outer aspect of the leg to the foot. Shortly thereafter she developed dependent swelling of both ankles, a feeling of "pins and needles" in the toes and feet, and weakness of the legs. The latter symptoms progressed in severity, so that by March, 1953, she was unable to walk without support. At that time an *x*-ray examination disclosed a lesion of the sacrum and she was admitted to another hospital, where she remained until her transfer to the Massachusetts General Hospital. Three weeks before the latter admission she began to have pain in the forearms and weakness of the hands. She had lost 30 lb. weight in a year.

Physical examination in June, 1953, disclosed striking evidence of weight loss. There were no abnormalities of the heart, lungs, or breasts. The liver edge was palpable 6 cm. below the right costal margin. Pelvic examination was normal excepting for the presence of a cystocele and rectocele.

The patient's mental state was considered normal, as were the cranial nerves. There was a great loss of motor power, affecting all the muscles of the trunk and the limbs. She was unable to sit unsupported and could barely retract her head. All movements of the upper limbs were freely performed. There was no voluntary movement in the toes or feet, and only the slightest degree of flexion and extension was possible at knees and hips. The limbs were flaccid and somewhat wasted. The deep tendon reflexes were absent and the plantar response was neutral. There was no sensory loss in the upper limbs. In contrast, vibratory sense was lost in the toes, and diminished at the ankles, knees, and iliac crests. Position sense was impaired in the toes and intact at the ankles. Painful, thermal, and tactile sensibility was impaired but not lost over the dorsal and ventral aspects of the feet and to a level just below the knees. The sensory impairment was symmetrical and much more severe in the distal than in the proximal parts of the legs.

Laboratory examination on admission disclosed the following: Haemoglobin 11·8 g.; W.B.C. 8,400 (65% polymorphonuclears, 9% lymphocytes, 6% monocytes); total protein 5·6 g. with an albumin-globulin ratio of 3·7 to 1·9. The blood serology was negative. Alkaline phosphatase was 3·2 Bodansky units (normal 0-5). Urine showed a specific gravity of 1018, but no albumin or other abnormalities. Radiological examination of the lumbar spine and pelvis revealed an extensive area of bone destruction and new bone formation. The lesions involved the upper part of the body and greatest part of the right wing of the sacrum. The sacro-iliac joint appeared preserved. Areas of increased density were also seen in the upper end and shaft of the left femur, in the left ischium and in the right ischium. There was also a sclerotic area in the anterior portion of the right sixth rib. It was thought that these lesions represented bony metastases of a mixed osteolytic and osteoblastic type. The remainder of the bony skeleton showed no focal involvement and there was no generalized osteoporosis. The stools were negative for blood and a barium enema revealed no abnormalities. The spinal fluid was under an initial pressure of 200 mm. of water; dynamics were normal, there were no cells but the protein content was 195 mg. %. Because of this finding the lumbar puncture was repeated several days later, at which time the protein was 210 mg. %. Spinal fluid dynamics were again normal, as were lumbar, thoracic, and cervical myelograms. By July 13 the spinal fluid protein was 260 mg. %. Samples of marrow from the sternum and the iliac crest were not considered abnormal; the plasma cells were 2% in number and of the adult type.

On July 17 a biopsy of the sacrum was taken. A destructive lesion was encountered which had eroded through the outer cortex in several spots, especially near the right sacro-iliac joint. The tissue within the lesion was friable, grey, gelatinous, and homogeneous in appearance. It did not bleed. The microscopic examination revealed masses of loosely arranged cells supported by fibrous bands which were rich in capillaries. The cells were generally oval or polyhedral and varied considerably in size. The cytoplasm was moderately basophilic, and whereas the majority of the nuclei were round or oval, others were elongated or bilobed. The nuclei were generally eccentrically located and contained a coarse network of chromatin. Many binucleated cells were seen. There were collections of eosinophilic material around the blood vessels suggesting amyloid, but Congo red staining was negative. This tumour was considered to be a myeloma.

On August 4, 1953, treatment with cortisone was begun. One week later a course of *x* rays to the sacrum was instituted, 300 r per day for six days. The neuropathy remained unaffected, although pain was alleviated. On August 11, the spinal fluid protein level had risen to 340 mg. %. Films of the skeleton and skull were repeated but no lesion other than those originally reported could be seen. A Congo red test was done on August 12 and repeated on September 29; they showed that in the serum 57% and 50% of the dye was retained respectively.

Electrophoretic fractionation of the serum and the spinal fluid was carried out. The serum pattern was 44% albumin, 6% α_1 globulin, 13% α_2 globulin, 13% β_1 globulin, 15% β_2 globulin, and 9% γ globulin. This was interpreted as showing an increase in the β_2 component, the corresponding percentages for a normal control subject being 55, 5, 9, 13, 7, and 11 respectively. Electrophoretic fractionation of the spinal fluid disclosed values of 71, 10, 3, 7, 1, and 8 respectively; these figures are within normal limits.

Gradually and slowly the neuropathy progressed. By early November, 1953, only slight movement was possible at the shoulders and none in the arms and legs. By this time, sensory loss had become prominent in the arms.

Position sense was lost in the fingers and impaired at the wrists; vibration was barely perceived at the elbow; painful, thermal, and tactile sensation was impaired symmetrically in the hands and arms up to the elbow. As in the legs, the sensory affection was most severe in the distal portions. Repeated radiographs up to the time of death showed no change in the skeletal lesions. The diaphragms moved poorly. On December 20, 1953, the temperature rose to 104° F., respirations to 40 per minute, and signs of consolidation appeared in the right lower lobe. The patient died on December 27, 1953.

General Pathological Findings.—The necropsy was performed eight hours after death. There was less than the normal amount of subcutaneous fat. Numerous enlarged axillary and inguinal lymph nodes were palpable. There were numerous soft lymph nodes, 1-2 cm. in diameter, in the mesentery and around the bronchi. The lower lobes of both lungs were firm and congested and sections of these portions of the lung showed numerous small areas of consolidation. The heart was not remarkable excepting for a brownish discoloration of the sectioned muscle. The liver weighed 1,850 g. The surface and cut sections showed diffuse yellow markings. A survey of the vertebrae and ribs revealed no bony lesions, with the exception of the sacrum and right iliac bone, which contained numerous foci in which bone was replaced by pinkish-grey friable tissue.

Microscopically the sacral tumour mass was identical with the biopsy material. No amyloid was seen. A section of rib marrow disclosed masses of tumour cells similar to those in the sacral tumour. Also the sinusoids of the spleen and many of the lymph nodes were filled with poorly differentiated plasma cells.

The heart, pancreas, and adrenal were normal. In the lungs there was severe congestion and oedema throughout the parenchyma. Many of the bronchioles were dilated and filled with an exudate consisting chiefly of polymorphonuclear leucocytes. Many alveoli contained a similar exudate. There was a slight to moderate congestion throughout the liver parenchyma and the sinusoids were generally dilated. The architecture of the kidney was well preserved. There were small focal areas of subcortical fibrosis and round cell infiltration. Some tubules contained hyaline casts, others contained a bluish-purple material suggesting calcium.

Neuropathological Findings.—The brain weighed 1,350 g. and appeared entirely normal. The spinal cord was removed in its entirety, and there was no evidence of compression at any point. The dura, cord, roots, and ganglia were grossly normal. The nerves of the legs were followed from their origin to their termination and showed no evidence of infiltration or compression. They were of approximately average size. All the skeletal muscles were light red and atrophic. The muscles in the extremities were more affected than those in the trunk. Coronal sections of the brain after fixation in formalin were normal.

Microscopic examination of the cerebrum and brainstem was normal excepting for a mild and questionable swelling and chromatolysis in the gracile and cuneate nuclei in the medulla. Blocks of tissue from the spinal cord, roots, ganglia, peripheral nerves, and muscle were fixed in formalin and embedded in celloidin or paraffin. Representative sections were prepared also by the frozen section technique. The stains employed were cresyl violet, haematoxylin and eosin, phosphotungstic acid, haematoxylin, oil red 0, Congo red, periodic-acid-Schiff, and crystal violet; appropriate sections were also stained by the methods of Spielmeyer, Loyez, Cajal, Bielschowsky, Bodian, and Van Gieson.

At all levels of the spinal cord a change in the posterior funiculus was evident. It was characterized by a loss of myelinated fibres and by gliosis in the columns of Goll and Burdach (Fig. 1B). The anterior horns showed an axonal reaction, most prominent in the lumbo-sacral and cervical regions. Most of the cells were swollen and chromatolytic with eccentric nuclei and a few of them had been replaced by glia (Fig. 2A).

There was marked disintegration of myelin in both the anterior and posterior roots, more prominent in the former and more in the distal than in the proximal portions (Fig. 3). The large fibres were more severely affected than the small ones. These changes, like the axonal reaction, were most marked in the lower lumbar and sacral roots, next in the cervical and upper thoracic roots, and least in the lower thoracic and upper lumbar roots. The myelin destruction was patchy in distribution and in these areas there was interruption of axis cylinders and invasion by macrophages. There was a mild lymphocytic infiltration here and there in both anterior and posterior roots. No plasma cells were seen in the nerves.

In the dorsal root ganglia there was a moderate degree of cell loss. Some of the ganglion cells were replaced by nests of cells with either oval or pleomorphic nuclei, the residual nodules of Nageotte. The oval or polyhedral cells in these clusters seemed to have been derived from proliferating satellite cells (amphicytes). Some of the surviving ganglion cells were frayed or angular in appearance and around them the satellite cells had increased to a marked degree. Between these cells there was a mild lymphocytic infiltration. These cellular changes were most marked in the sacral ganglia but were present to some extent in all. Many of the medullated nerve fibres and axis cylinders in the central parts of the ganglia had disappeared and numerous fatty macrophages were present (Fig. 2B).

All of the peripheral nerves studied showed degeneration of the medullated fibres. In general, the affection was more severe in the nerves of the extremities than in those of the trunk and more severe in their distal than in their proximal segments, just as it was in the roots. The large fibres were more affected than the smaller ones. Here, however, rather few fatty macrophages were seen in the areas of myelin disintegration, presumably because of the chronic nature of the process. Many of the axis cylinders had disappeared in the areas of myelin degeneration and many of those remaining were fragmented. In the sciatic nerve, both in the distal and proximal parts, not a single large fibre could be seen. The changes in the ulnar nerve were not as severe as those in the sciatic or femoral, but degeneration of the large fibres was prominent. In the ulnar nerve, masses of disintegrating myelin in the form of ovoids were invaded by macrophages;

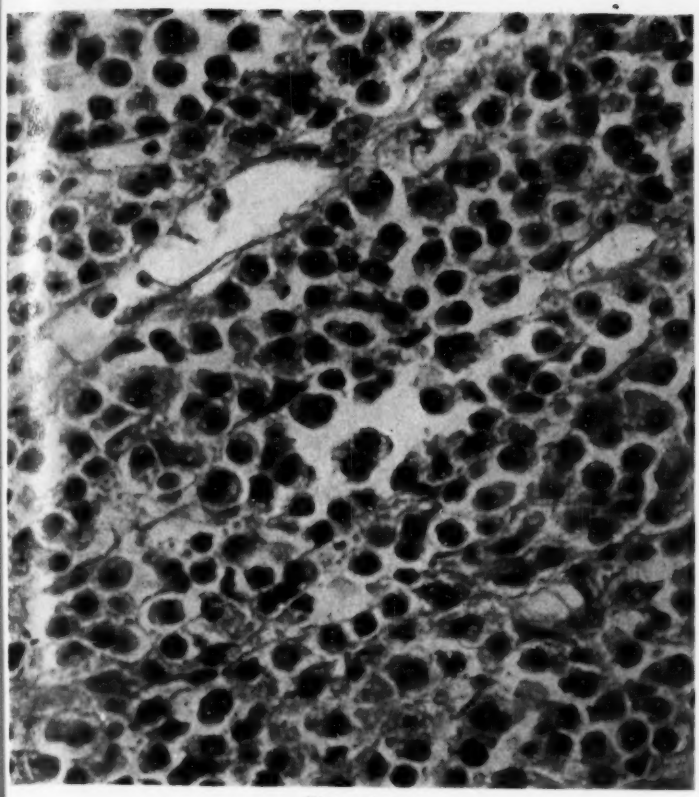

FIG. 1A

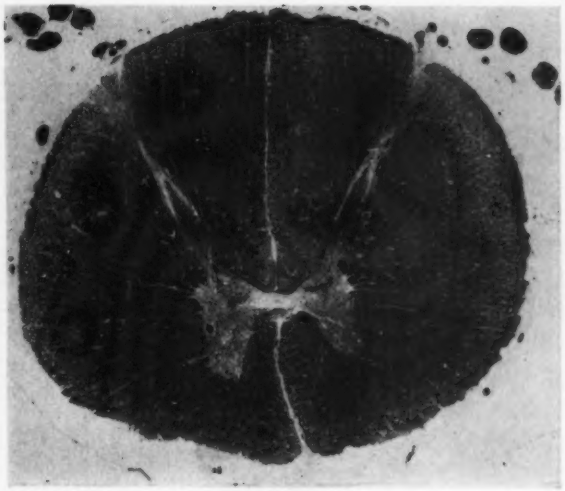

FIG. 1B

FIG. 1.—A. Case 2. A section from the tumour of the first lumbar vertebra. The tumour is composed of a homogeneous mass of mature plasma cells. Hematoxylin and eosin stain. ×380.
B. Case 1. A transverse section of the sixth dorsal segment of the spinal cord, showing pallor of the columns of Goll. Loyez myelin stain. ×18.

FIG. 2.—A. Case 1. Spinal cord at the C2 level, showing swelling, chromatolysis, and eccentricity of nuclei in the anterior horn cells. Cresyl violet stain. ×60.
B. Case 1. Spinal ganglion at C7 segment showing loss of cells and an occasional "residual nodule of Nageotte". A vascuolated cell is seen in the lower left corner. Loyez myelin stain. ×45.

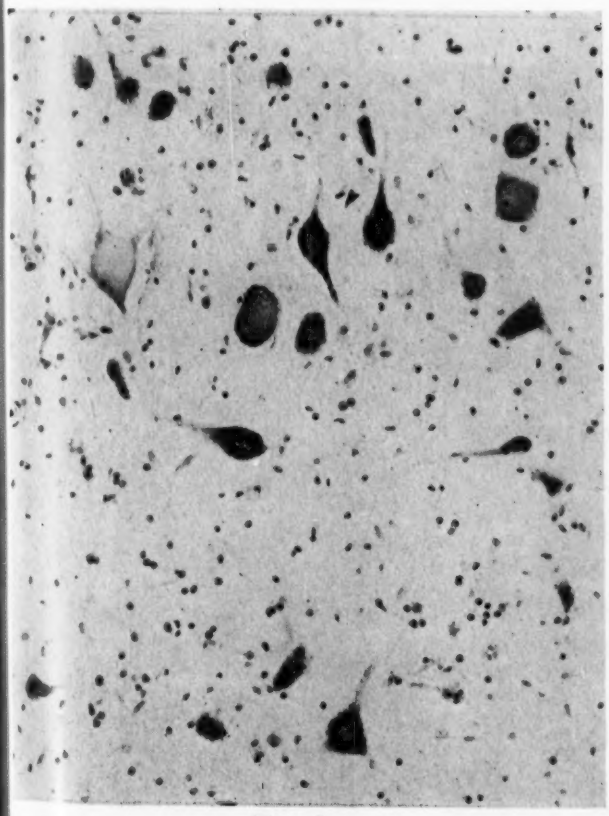

FIG. 2A

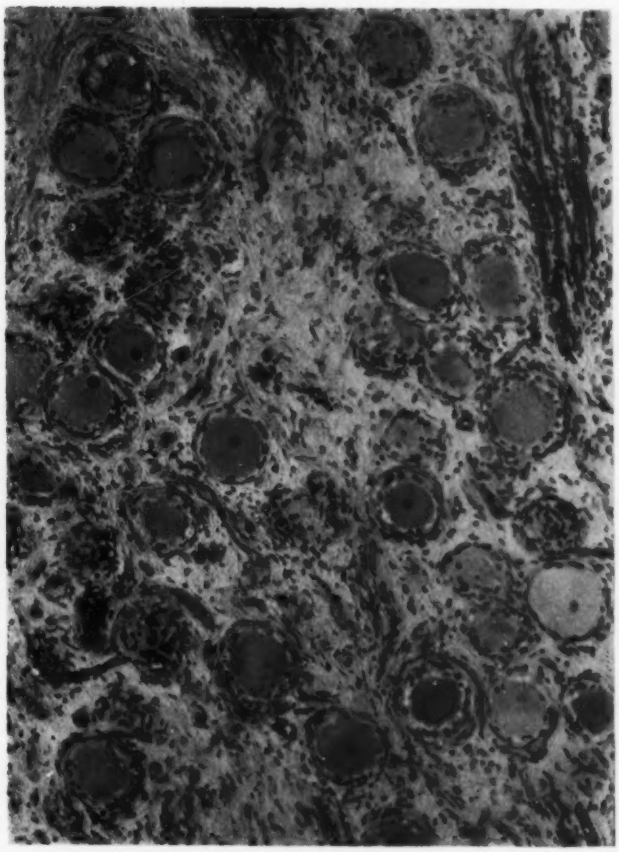

FIG. 2B

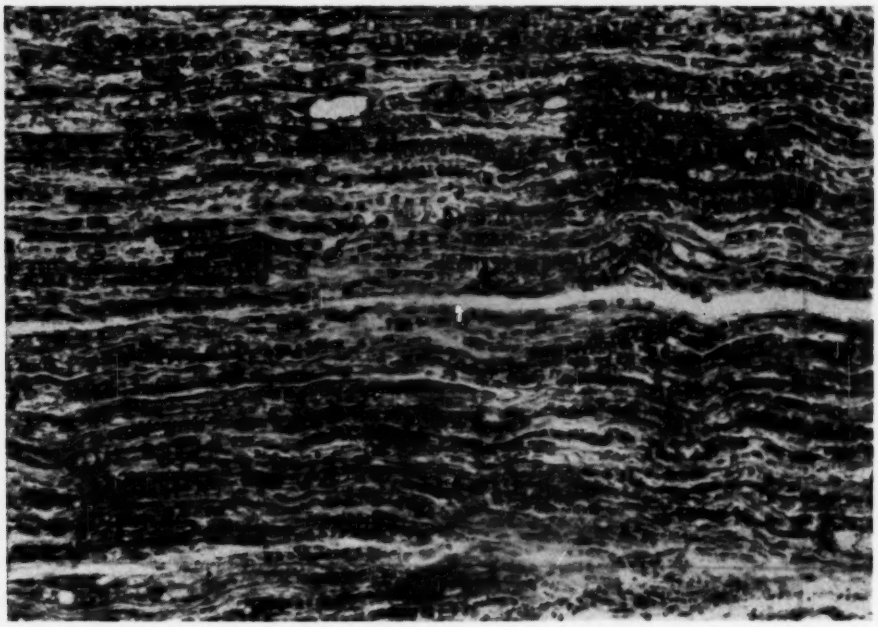

FIG. 3A

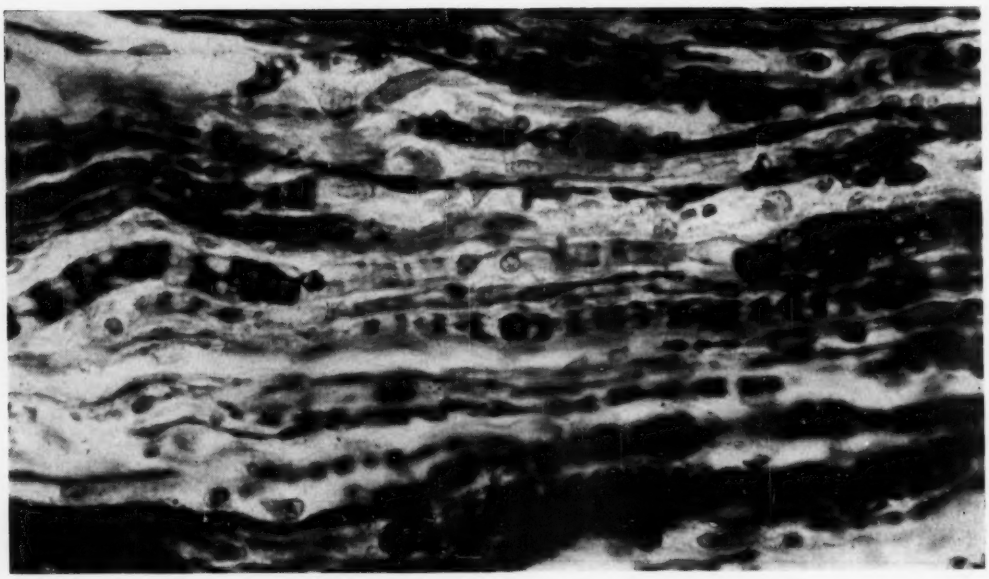

FIG. 3B

FIG. 3.—Case 1. The first sacral posterior root (A., ×70) and anterior root (B., ×300), showing the patchy destruction of myelin. Spielmeyer myelin stain.

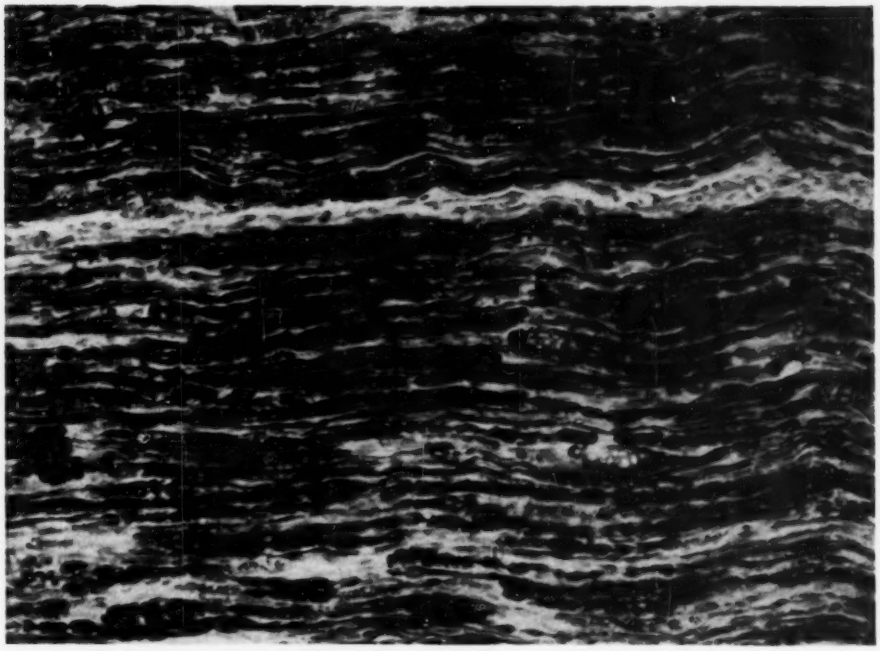

FIG. 4A

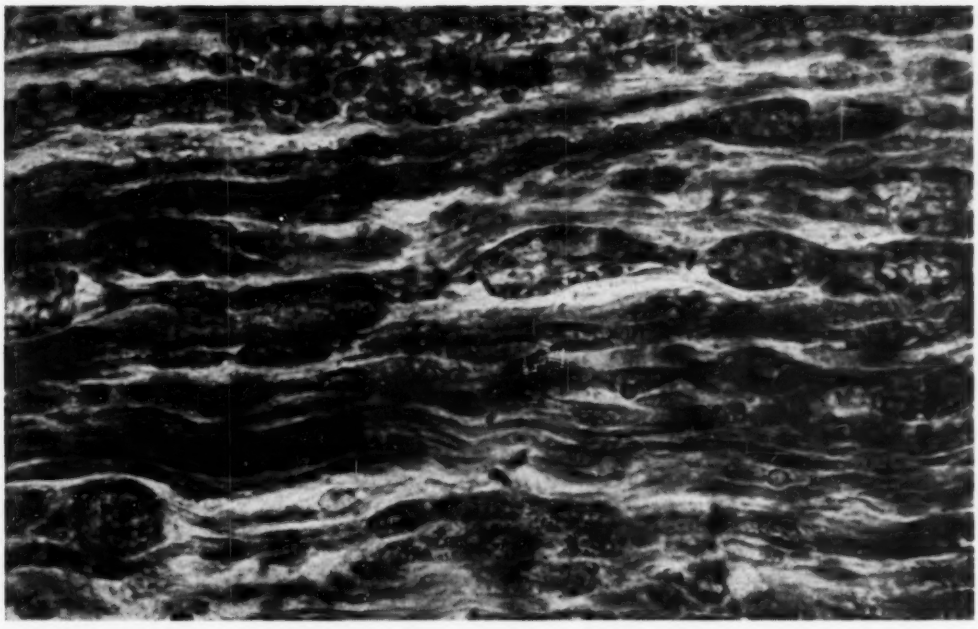

FIG. 4B

FIG. 4.—Case 2. A. A posterior root (Spielmeyer myelin stain. × 100) and B., an anterior root (oil red O stain. ×380). In both of these sections the segmental degeneration of myelin is evident.

FIG. 5A

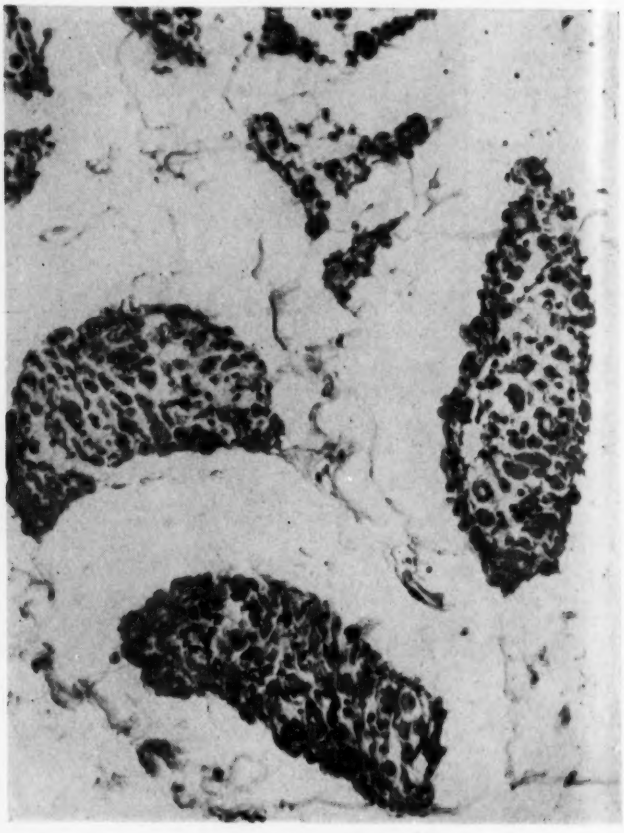

FIG. 5B

FIG. 5.—A. Case 3. A section of the right common peroneae nerve, showing a loss of some fibres and others undergoing degeneration. Spielmeyer myelin stain. ×300.

B. Case 1. A section of the vastus lateralis muscle showing an advanced degree of neural atrophy. Hematoxylin and eosin stain. ×200.

and some of these ovoids contained particles of axoplasm—so-called digestion chambers. Here and there in sections of nerves stained by the Bodian method, numerous small, delicate strands were seen which were taken to be regenerating axones. In the cross sections of nerve, an interesting change was seen involving veins, arterioles, and small arteries. The vessels walls were thickened, and the lumina were narrowed by intimal hyperplasia but all were patent. Occasional vessels were surrounded and infiltrated by lymphocytes and mononuclear cells. In numerous sections stained by Congo red, P.T.A.H., crystal violet, iodine, and periodic-acid-Schiff methods, no amyloid could be identified.

All the muscles of the extremities, and to a lesser extent of the trunk, showed the picture of far advanced neural atrophy (Fig. 5B). The muscle fibres were reduced to thin ribbons of sarcoplasm and the sarcolemmal nuclei were relatively increased. In some places the fibres had disappeared entirely, and only darkly stained cells were found in rows within the thin sarcolemmal tubes. In places, even the tube was absent and small groups of dark nuclei appeared to lie within the fibrous tissue. The blood vessels showed the same changes as described in the blood vessels of the nerves.

Case 2.—W. E. McD., a 48-year-old linotype operator and former parachutist, was admitted to the Boston Veterans Administration Hospital on August 18, 1952. About nine months before he had noted weight loss, he became easily tired, and had low back pain. Examination at that time disclosed the presence of haemorrhoids and in December, 1951, a haemorrhoidectomy was performed under caudal anaesthesia. His post-operative course was uneventful, although his general symptoms failed to improve. About one month after the operation there was a gradual onset of numbness and weakness of the legs. These symptoms progressed rapidly and by April, 1952, he was unable to stand or walk unaided.

About this time similar symptoms appeared in the hands. Examination in April, 1952, revealed evidence of advanced neuropathy. The hip musculature had only about 50% of normal power, the thigh muscles somewhat less, and the lower leg muscles were completely paralysed. There was a slight weakness of the para-spinal muscles, and in the arms the only weakness was in the hands. The affected muscles were atrophic and tendon reflexes were abolished. Painful and tactile sensibility was impaired in the hands and feet.

In May, 1952, he suffered an attack of severe abdominal pain and a cholecystostomy was performed at another hospital. Recovery was delayed by the drainage of bile from the operation site.

By the time of his final hospital admission in August, 1952, he had lost 40 lb. in weight. Examination at this time disclosed a severe degree of muscle wasting and a fistula at the upper end of the cholecystostomy scar. The skin over the lower legs and sacrum was shiny and erythematous and the remainder of the skin appeared tanned. There were no abnormalities in the mental sphere or in cranial nerve function. All the muscles of the lower limbs were paralysed and extremely atrophic with contractures at the knees and ankles. The intrinsic muscles of the hands were atrophic, those of the forearm less so, and there were flexion contractures of the fingers and wrists. Only weak movements of flexion and extension were possible at the elbows and of abduction and adduction at the shoulders. The deep reflexes were absent throughout and the plantar responses were neutral. Superficial sensation was lost over the feet and was impaired to some extent as high as the hips. Vibration and position sense were lost in the hands, in the lower limbs, and in the ankles, knees, and hips.

Laboratory examination disclosed the following: Haemoglobin 13·5 g. %; W.B.C. 7,500 with a normal differential count; the urine was normal except for occasional red cells in the sediment; the cerebrospinal fluid pressure and dynamics were normal and showed 3 lymphocytes, sugar 75 mg. %, chlorides 120 mEq. per litre, total protein 90 mg. %, and a normal colloidal gold reaction; the blood and cerebrospinal fluid Wassermann reactions were negative. There was free acid in the gastric aspirate. The total protein of the blood was 5·1 g. %, but otherwise the blood chemistry was normal.

Shortly after the patient's admission to the Veterans Administration Hospital a chest film revealed an infiltration in the left lower and mid-lung fields. He was treated with penicillin and intravenous fluids, but he continued to have fever, dyspnoea, and increasing signs of pulmonary consolidation. Bronchoscopy was performed but no obstruction was found. The patient became afebrile on large doses of penicillin and streptomycin, but because of the large amount of secretions and the inadequacy of his cough he required almost continuous bronchoscopy. He died on October 1, 1952, of respiratory failure.

General Pathological Findings.—There was a marked depletion of fat in the omentum and mesentery; the serosal surface of the small bowel presented a spotty, dull, granular appearance; four greyish, firm, retroperitoneal nodes measuring 1·5 cm. in diameter and several similar nodules in the mesentery of the small bowel were seen. There were adhesions between the duodenum, transverse colon, and the gall bladder, and a small pocket of pus beneath these. Approximately 140 ml. of greenish-yellow fluid was found in the left pleural cavity, and there were firm fibrous adhesions between the left lung base and the diaphragm. The right lung weighed 500 g., the left 650 g. The trachea and main stem bronchi contained a considerable amount of purulent, tenacious, greenish-white material and the bronchus leading to the left lower lobe was completely occluded by this material. The left lower lobe was firm and not aerated; on section it was purple, and the bronchi exuded purulent material.

Microscopically, the alveoli contained numerous macrophages and occasional polymorphonuclear cells. The alveolar walls appeared thickened. Other sections showed emphysema and atelectasis. The heart and valves were essentially normal. In the abdominal aorta there were scattered atheromatous plaques. The spleen weighed 240 g. The capsule was wrinkled, dull grey, and adherent to the diaphragm. On section, it was soft and the corpuscular markings were accentuated. The liver weighed 2,100 g. but was otherwise normal. The gall bladder was adherent to its bed and contained two cholesterol stones measuring 2·5 and 1·8 cm. in diameter. The cystic duct was occluded by dense fibrous adhesions. The other portal structures were normal. The pancreas, adrenals, gastro-intestinal tract, genito-urinary system, and the thyroid were all normal.

Filling almost the whole body of the first lumbar vertebra was a well-circumscribed, soft, pink-white tumour mass measuring 2·7 cm. in diameter. It was delimited peripherally by a paper-thin, bony shell with a smooth grey lining. The tumour did not extend beyond the normal limits of the body of the vertebra, and compression of the cord by the tumour or by vertebral deformity could not be made out. Microscopic examination disclosed a homogeneous well-vascularized mass of mature plasma cells (Fig. 1A). There were only occasional cells with multiple nuclei; mitoses were lacking. There was a narrow zone of collagen around the capillaries. Unfortunately no other sections of the bone marrow were taken.

Neuropathological Findings.—No areas of rarefaction were seen in the calvarium. The brain, which weighed 1,300 g., was examined after fixation in formalin. The dural sinuses were negative. In the fronto-parietal regions bilaterally the leptomeninges were thickened and of opaque whitish appearance. There was some slight generalized atrophy of the frontal lobes as indicated by narrowed gyri and widened sulci. The cerebral vessels showed minimal atheromatous changes. On serial sections of the brain, no abnormalities could be seen.

The dura over the spinal cord was somewhat thickened. There were no adhesions between the dura and arachnoid, and the inner surface of the dura and the surfaces of the spinal cord and roots were of normal appearance. The blood vessels in the cauda equina were rather large but not increased in number. A few roots of the cauda equina seemed unusually grey and thin. On sectioning the cord, no areas of softening, discoloration, or other abnormalities were found.

The most striking abnormalities were seen in the peripheral nerves. There was a loss of a large proportion of the medullated fibres, predominantly of the large ones and a relative increase in connective tissue. In the areas undergoing degeneration one could also see changes in the Schwann cell syncytium, with clumps of Schwann cells and fibroblastic nuclei and rare fatty macrophages. Here and there the peripheral nerve was infiltrated with mononuclear cells, mainly lymphocytes, but no plasma cells were seen. In the cross sections of the nerve, the blood vessels appeared slightly thickened; however, their lumina were patent. No amyloid could be demonstrated.

In the spinal nerve roots there was definite evidence of disease, somewhat more in the posterior than in the anterior ones (Fig. 4). The large fibres and some of the medium-sized ones had disappeared, whereas most of the smaller fibres were well preserved. In addition, small clusters of very thin, poorly medullated or non-medullated fibres were embedded in small clumps of connective tissue. There was little evidence of Wallerian degeneration. Some of the intact fibres were abnormal, in that their myelin sheaths had disappeared in segments for distances of 150 to 200μ, leaving bare axis cylinders. In places where medullated fibres had disappeared the axis cylinders were also fragmented or were no longer visible. Ellipsoids and ovoids of myelin were still present. In the cauda equina both in the anterior and posterior roots there was a diffuse infiltration of mononuclear clear cells, predominantly lymphocytes.

In the sensory ganglia some of the cells were round and pale, and there were large numbers of fibroblasts and many fat-containing histiocytes. Some cells had disappeared completely and were replaced by the "residual nodules of Nageotte ".

In many of the anterior horn cells of the spinal cord there was an axonal reaction, especially in the more laterally placed cells of the lumbar and cervical segments. At the cervical level, the columns of Goll showed a slight loss of large fibres, with an increase in astrocytes in this region. Microscopically, there was no evidence of arachnoiditis.

The muscles of the limbs showed a marked denervation atrophy. No abnormalities were observed in the microscopic sections of the brain.

Case 3.—Mrs. S. G., a 58-year-old woman, was first admitted to the First (Tufts) Medical Service of the Boston City Hospital on June 27, 1952. She had been well until four months before, when severe and persistent pain in the shoulders, chest, low back, and legs began. Over the four-month period she had suffered from general weakness and night sweats and had lost 20 lb. in weight. Other symptoms included frequency and burning pain on urination, lightheadedness, and exertional dyspnoea, all of which had become progressively worse until the time of her admission to the hospital.

Examination disclosed an obese and somewhat dyspnoeic woman. The vital signs were normal and the blood pressure 130/60 mm. Hg. There was a mild dorsal kyphosis, and slight tenderness over the right scapula and over the right lower chest anteriorly. The heart, lungs, and abdomen were essentially normal. There was no loss of muscle power or atrophy. Reflexes were brisk and equal throughout; the plantar responses were flexor, and no sensory loss could be discerned.

Radiographs disclosed multiple, rounded areas of radiotranslucence in the bones of the skull, fractures of several ribs, and diffuse destruction of the bones of the spine, pelvis, and upper femurs. The urine showed a constant albuminuria and occasionally red cells, white cells, and granular casts in the sediment. No Bence-Jones protein could be detected. A blood count on June 27, 1952, was as follows: R.B.C. 3·44 million; haematocrit 34; haemoglobin 10·5 g. %; W.B.C.s 8,250 with a normal differential. The blood serology was negative. The total protein level was consistently elevated, up to 9·8 g. on one occasion. with an albumin-globulin ratio of 4 to 5·8. The serum calcium level was 6 mg. %, phosphorus 9 mg. %, and the alkaline phosphatase was 4·7 units. The non-protein nitrogen was consistently elevated, fluctuating between 136 and 240 mg. %. The sternal marrow contained clumps of atypical plasma cells, many of them showing the characteristics of the " myeloma cell ".

Treatment with urethane was instituted, but the patient was unable to tolerate this drug, and it had to be discontinued. However, she improved spontaneously and was discharged on August 30, 1952. On September 8, 1952, she returned to the hospital because of the manifestations of tetany. The symptoms responded well to treatment with intravenous calcium gluconate and sodium bicarbonate, and she was discharged on September 16, 1952.

The patient returned to the hospital for the last time on April 11, 1953. For several months preceding this final admission she had suffered from generalized pains and persistent vomiting. In addition she had noted a specific weakness of the legs, progressive in nature, so that she was unable to walk for any distance and was finally confined to bed. Examination on this admission, in addition to the abnormalities previously noted, revealed a softened area in the right frontal bone measuring about 4 cm. in diameter, and an enlarged liver, the edge being palpable 4 cm. below the right costal margin. The patient was alert, cooperative, and well orientated. The cranial nerves were judged to be entirely normal. There was an advanced degree of atrophy of the legs, more marked on the left, and weakness of dorsiflexion, eversion, and plantar flexion of the feet, also more marked on the left. Muscle power in the arms was adequate. There was a fine tremor of the extended hands. The tendon reflexes were brisk and equal throughout, excepting at the ankles, where they were absent bilaterally. The plantar responses could not be interpreted accurately because of withdrawal responses. Below the knees, there was a diminution of tactile, pain, and vibratory sensations, and position sense was impaired in the toes. The patient was now markedly anaemic; the non-protein nitrogen was 220 mg. %, and the CO_2-combining power was 25 vol. %. The cerebrospinal fluid pressure and dynamics were normal; the fluid contained 4 lymphocytes and a total protein of 45 mg. %. The colloidal gold was normal. Despite

transfusions of whole blood the patient died on April 17, 1953.

General Pathological Findings.—A necropsy was performed 19 hours after death. The marrow of the ribs, sternum, vertebrae, and iliac bones was pale, with light tan, soft, fatty areas scattered throughout. The mitral and aortic valves showed many small calcified nodular areas. The lungs were increased in weight (right 800 g.; left 600 g.). On section, both lower lobes showed a lack of crepitation and a deep reddish appearance and they were slightly greasy to the touch. The kidneys each weighed 300 g., and the cut surfaces showed marked pallor and poor corticomedullary demarcation. In the para-aortic area there were eight to 10 firm, greyish-white lymph nodes, 1·5 cm. in length.

Microscopically, the heart muscle showed marked fatty infiltration throughout. The liver cells were poorly preserved, with fat-containing vacuoles of varying size in their cystoplasm. Throughout the lungs, but mainly in the lower lobes, many of the alveoli were collapsed, others contained macrophages, and the vessels in the alveolar walls were congested with red cells. In the kidneys, many of the tubules were filled with granular casts, and in many areas these tubules were surrounded by foreign body giant cells and small numbers of neutrophils. Many of the glomeruli and tubules were absent and replaced with fibrous tissue. Sections through the sternal, costal, vertebral, and iliac bone marrow all showed varying degrees of infiltration with cells of the plasma cell type. These cells had eccentric nuclei and some had two nuclei. The basi-chromatin of the nuclei was arranged in clumps. The cytoplasm stained a lavender colour with haematoxylin and eosin, and often the perinuclear zone was lighter in colour than the remainder of the cytoplasm.

Neuropathological Findings.—Because of restrictions placed on the post-mortem examination, the brain was not examined. The spinal cord and roots appeared grossly normal, with no evidence of compression or infiltration by tumour. There was a haemorrhage which appeared to be of recent origin in the right common peroneal nerve.

In the spinal cord there was a slight loss of myelinated fibres in the columns of Goll and Burdach, with a slight increase of astrocytes in this region—a replacement gliosis. In the lumbo-sacral region of the cord, the more laterally placed anterior horn cells showed a typical axonal reaction, about one-third of the cells being affected in this manner.

In both the anterior and posterior lumbo-sacral roots the myelin sheaths were conspicuously altered. The larger myelin sheaths were fragmented and some of these fragments were expanded or ballooned, and at the nodes of Ranvier there was extensive retraction leaving gaps in the sheathing and a short stretch of naked axis cylinder. In some fibres the myelin disintegration could be followed for a considerable extent, in others it involved only short segments. In the areas of myelin disintegration there was also some loss and destruction of axis cylinders.

In the dorsal root ganglia there was only a mild degree of abnormality of the cells. Some cells had evidently disappeared and had been replaced by residual nodules; others appeared swollen and chromatolytic, with an increase of satellite cells in the subcapsular space. Histiocytes, some of which contained fat, were seen in the residual nodules and here and there in the centre of the ganglia. The axis cylinders within the ganglia were tortuous and dilated.

In the more proximal parts of the femoral, peroneal, and tibial nerves, there was relatively little change in some places except for isolated fibres which were undergoing degeneration (Fig. 5A). In some of these fibres, the myelin degeneration could be followed for a considerable extent, in others it was circumscribed. In the intact fibres, except for minor alterations in the myelin sheath and a slight increase in the number and size of the Schwann cells, there was little change of importance. In the right common peroneal nerve the haemorrhage had undergone fibroblastic organization; in this area the walls of the blood vessels were infiltrated with inflammatory cells, mainly polymorphonuclear leucocytes. In general the arteries and arterioles in and around the nerves were hyperplastic, their lumina were narrowed, and a few of the vessel walls appeared hyalinized. However, there was no evidence of infiltration with amyloid. Muscle tissue was not available for microscopic examination.

Case 4.—C. D., a 47-year-old man, was first seen on the First (Tufts) Medical Service of the Boston City Hospital on September 22, 1947, complaining of numbness of the hands, burning sensations of the feet, and drawing pains in the legs of about six months' duration. In addition he had lost 25 lb. in weight in the year preceding admission. The physical examination at that time was normal in a general sense, although he was mildly anaemic (R.B.C.s 3·91 million, haemoglobin 72%). On neurological examination, forward bending of the neck was slightly limited, this movement producing pain and paresthesiae in the arms and back. There was slight tenderness over the seventh cervical spine. Tactile sensation was impaired over the fingers. Position sense was defective but not lost in the toes, and vibration sense was diminished below the level of the first lumbar vertebra. Deep reflexes were normally active, and the plantar response was flexor bilaterally. A lesion of the cervical cord was suspected, but none could be found despite a careful search. Radiographs of the spine and skull were normal. Lumbar puncture disclosed clear and colourless cerebrospinal fluid. The initial pressure was normal as was the response to jugular compression. Seventy-two cells were reportedly found, predominantly lymphocytes. Total protein was 222 mg. % and the colloidal gold curve was 0122333332. The Wassermann reaction in the cerebrospinal fluid was negative. Lumbar puncture was repeated on October 6. The protein was 174 mg. %, but no cells were found on this or subsequent examinations. A cervical myelogram performed on this occasion was normal.

During the next several months there may have been a slight degree of spontaneous improvement in the numbness and tingling of the extremities, and a gain in weight; certainly the disease did not progress. The patient

remained in this state until February, 1948, when, because of a worsening of the paresthesiae and the onset of a constrictive abdominal sensation, he was readmitted to the hospital. The neurological examination was the same as previously, except that on this occasion forward flexion of the neck did not result in paresthesiae of the arms and legs.

Laboratory examination revealed many new abnormalities. There was a consistent albuminuria and occasional white and red cells in the urinary sediment. The blood proteins were elevated, on one occasion as high as 9·25 g. %, with an albumin-globulin ratio of 4 to 5·25. The cerebrospinal fluid protein was 200 mg. %, and the dynamics were normal on two separate tests. The findings in the blood were: R.B.C.s 3·86 million, haematocrit 37%, haemoglobin 11·4 g. %, with normocytic indices.

An aspiration of the sternal marrow disclosed 19% plasma cells, many of which were multinucleated and characteristic of " myeloma cells ". A sternal marrow biopsy also disclosed an increased number of plasma cells, many in clumps. Finally, on March 31, 1948, Bence-Jones protein was discovered in the urine. A diagnosis of multiple myeloma was made and urethane therapy, 3 g. daily, was instituted.

For the following two years the patient was admitted to the hospital many times, mainly for readjustment of the urethane dosage, and on one occasion for an illness presumed to be infectious hepatitis. In May, 1948, he received a series of injections of stilbamidine, 150 mg. every second day, to a total dosage of 1,300 mg. In October, 1948, he developed facial paresthesiae, which gradually receded over the ensuing months. Throughout this two-year period he continued to complain of severe constricting pains around the lower costal margin, and of cramping pain in the thighs. In the course of this time blood values returned to normal, but the neurological signs remained unchanged, and the cerebrospinal fluid protein level ranged between 133 and 174 mg. %.

The patient was readmitted to the hospital on March 16, 1950, because of increasing stiffness of the legs and difficulty in gait and persistence of the girdling sensations of the lower chest and abdomen. On examination it was noted for the first time that his gait was unsteady and " high stepping " in character. There was marked weakness of dorsiflexion of both feet, and a moderate degree of wasting of the anterior tibial and peroneal muscles of both legs. Ankle jerks were depressed. There was also a mild, distal blunting of pain sensation in the legs, and a diminution in vibratory sensation at the iliac crests and below. Once again the spinal fluid dynamics were normal, but the protein was 95 mg.%. A radiological survey of the lumbar vertebrae and other parts of the skeleton revealed no bony lesions of significance. He was given a course of intravenous urethrane therapy, but the weakness of the feet increased, and the ankle jerks were lost entirely. In May, 1951, urethrane therapy was discontinued, never to be resumed. Between May and October, 1952, he received *x*-ray treatment to the spinal column, in the belief that the myeloma had seeded itself along the lumbo-sacral roots. Nevertheless, weakness increased and his gait deteriorated progressively. By October, 1952, he required a cane to get around. He was unable to rise on his toes, nor could he rise from a squatting position. There was now a marked weakness of both the flexor and extensor muscles of the feet and moderate weakness of the knee and hip musculature. The ankle jerks were absent and the knee jerks could barely be obtained with reinforcement. The plantar responses were neutral. The wasting of the calf and anterior tibial muscles was more pronounced than previously. Position sense was lost in the toes and vibration sense was lost at the iliac crests and below. There was also a symmetrical loss of painful and tactile sensations over the feet. Motor, sensory, and reflex functions were entirely normal in the upper limbs. Once again the spinal fluid dynamics were normal and the protein content was 103 mg. %.

The patient has been seen periodically, the last time in April, 1957. Over a six-year period the neuritic signs have progressed only slightly. In general he feels well and the blood constituents are maintained at normal levels. In January, 1952, a compression fracture of the fourth lumbar vertebra was discovered radiologically. There were no new neurological signs, however, and subsequent films of the lumbar region and the entire skeleton have failed to disclose any further bony changes.

In January, 1952, a biopsy was taken of the left superficial peroneal nerve and neighbouring muscle. At operation this nerve seemed to be larger than normal, 3-4 mm. in diameter. It appeared greyish and " watery " in colour. Manipulation of this nerve during the section did not provoke the pain that one is accustomed to excite in such manoeuvres.

Microscopically, only a few medullated nerve fibres remained in the nerve. There was degeneration of both the myelin and axis cylinders of most of the fibres, with fibrous tissue replacement. Most of the muscle fibres were small but there were isolated groups of normal-sized fibres as well. There was a relative increase in connective tissue.

Case 5.—W. R., a 54-year-old man, a patient of Dr. William C. Maloney, was admitted to the Cambridge City Hospital, Cambridge, Massachusetts, on March 25, 1947, complaining of pains in all the joints of the extremities of one year's duration. Two weeks before this admission he developed a particularly severe pain in the right shoulder, with radiation into the hand and the right side of the chest. He had suffered from a chronic, slightly productive cough, but otherwise his past and family histories contributed nothing. Examination disclosed a generalized muscular tenderness and evidence of bronchopneumonia at the bases of both lungs. The laboratory examination showed the following abnormalities: Haemoglobin 9 g.%, R.B.C.s 2·7 million, W.B.C.s 4,500, with a normal differential count: marked albuminuria; total protein 7·2 g. with an albumin-globulin ratio of 2·6 to 4·6. The skull film was typical of multiple myeloma; there were multiple small round areas of radiance scattered throughout the fronto-parietal and occipital regions and the skull tables in general appeared decalcified. There were also small radiant defects in the ribs. About 40% of the sternal marrow cells were of the

plasma-cell type. The majority of these exhibited an eccentrically placed nucleus, deeply staining blue cytoplasm and vacuoles in the cytoplasm. Many of the cells were undergoing mitosis and a few contained nucleoli.

The blood Wassermann reaction was negative. Repeated testing of the urine failed to reveal Bence-Jones protein. A lumbar puncture showed normal cerebrospinal fluid pressure and dynamics, a total protein of 50 mg. % and a flat colloidal gold curve.

On May 12, 1947, urethane therapy, 3 g. daily, was instituted. Within two weeks the pain was markedly less, and in the ensuring months he was symptom free except for a mild, inconstant ache in the joints. By December, 1947, the blood values had returned to normal with the exception of the protein which was 8·3 g. with an albumin-globulin ratio of 3·8 to 4·5. The skull films showed the same abnormalities, but those in the ribs seemed to have cleared. The plasmacytosis of the sternal marrow was no longer present. Urethane therapy was stopped in September, 1949.

The patient was seen again on October 26, 1954, with complaints of tingling and "pins and needles" feelings in the hands and feet. He was unsure of the exact time of onset of the symptoms, but they had been constant for several years. Examination on this date revealed evidence of a mild but definite sensory loss, affecting the distal parts of the limbs in a symmetrical fashion. There was impairment of vibratory sensation in the toes and finger tips. Using a Von Frey hair, a weight of 20 mg. was required before the patient first perceived a touch stimulus at the mid-leg and at the metacarpophalangeal joints. With 40 mg. he was able to detect touch at the ankle and over the middle of the digits. A defect of pain and temperature sensation was also demonstrable. The sharpness of a 6 g. pin was not appreciated until points above the mid-forearm and above the mid-leg were reached. The impairment of temperature sensation corresponded to that of pain. Motor power was intact in the limbs, reflexes were sluggish, but all were present and equal. The plantar responses were flexor. An examination in April, 1955, disclosed very much the same abnormalities. A lumbar puncture done on this date showed the cerebrospinal fluid to be under an initial pressure of 130 mm. water and a final pressure, after the removal of 10 ml. of fluid, of 100 mm. water. The cerebrospinal fluid dynamics on jugular and abdominal compression were normal, there were no cells, and the protein level was 16 mg. %.

A biopsy was not performed.

Discussion

Reviewing briefly the salient clinical features of our cases it will be noted that three were males, two were females, and their ages at the onset of the illness ranged from 44 to 58 years. These figures reflect the age incidence and the predominance in males generally found in this disease. Three of our patients (Cases 3, 4, and 5) showed the classical features of multiple myeloma; their symptomatology was characterized by varying degrees of bone pain, anaemia, osteolytic lesions, hyperglobulinaemia, Bence-Jones proteinuria, and the presence of myeloma cells in the marrow. In Cases 3 and 5, these features were present from the onset of the illness, whereas in Case 4 they were only recognized six months after the onset of a perplexing neurological problem. In two patients (Cases 1 and 2) the symptoms of polyneuropathy dominated the clinical picture and the characteristic symptoms of multiple myeloma were either minimal and obscured (Case 1) or entirely unrecognized during life (Case 2). These two patients showed a number of other distinctly unusual features. Hyperglobulinaemia and Bence-Jones proteinuria were absent in both, although the serum electrophoretic pattern of Case 1 showed an elevation of the β_2 globulin. Repeated radiological and sternal marrow examination did not reveal evidence of disseminated myeloma. Neither of these cases, however, could be accepted as examples of a solitary plasmacytoma. In Case 2 a careful post-mortem examination of the marrow, aside from the lumbar vertebrae, was not made. In Case 1 post-mortem examination disclosed the presence of disseminated lesions in the form of masses of tumour cells in the rib marrow, as well as the presence of undifferentiated plasma cells in the sinusoids of the lymph nodes and the spleen. A most unusual feature of Case 1 was the radiological appearance of the sacral lesion: it was osteoplastic as well as osteolytic. Osteoplastic lesions are distinctly rare in this disease, and we are aware of only one report of a similar case (Krainin, D'Angio, and Smelin, 1949).

Two patients (Cases 4 and 5) have experienced a remarkable remission in symptoms. In these patients the symptoms of multiple myeloma have been present for over nine years, and at the time of writing both patients are well in so far as the symptoms of multiple myeloma are concerned, although the neuropathy is stationary or progressing very slowly. Since the average duration of life after the onset of symptoms is between 18 and 24 months (Snapper, 1952; Geschickter and Copeland, 1928), the long survival in these patients has proved of considerable interest and has formed the subject of a special report by Kenney and Moloney (1956). These authors point out that the patients who survive for many years have certain features in common, namely, the relatively small myeloma cell population in the bone marrow, myeloma cells of the mature type, and minimal renal, blood protein, and bone abnormalities. Although the cases reported by these authors were treated with urethane, they attribute the benign and chronic course to the natural history of the disease rather than to drug therapy.

The polyneuropathy, although varying in severity, took a characteristic form in four of our patients.

Essentially, it was a symmetrical, atrophic, areflexic, sensorimotor affection of the legs, and, in two cases, of the arms. In our first two cases the sensorimotor neuropathy affected all the limbs, and later the trunk as well. It was severe and progressive in nature and was responsible for the patients' deaths. In two other patients (Cases 3 and 4), the neuropathy was less severe in degree and more sharply limited to the legs. In Case 2, in which the myeloma was only discovered at post-mortem examination, the clinical picture was similar to that described by Scheinker (1938), in which a plasma cell tumour of the sternum was discovered at necropsy in a patient who had suffered from a progressive neuropathy for two years. Another patient (Case 5) presented a mild sensory polyneuropathy which has remained stationary for about six years.

There was a striking lack of parallelism between the symptoms of neuropathy and those of myeloma. In Cases 1 and 2 the clinical pictures were essentially of severe and ultimately fatal polyneuropathy, and the usual symptoms of myeloma were lacking. In these two cases the diagnosis of multiple myeloma was only established by the biopsy of an unsuspected bone lesion and by post-mortem examination respectively. In Case 3, the symptoms of neuropathy were restricted and relatively mild, and had developed in the course of a rapidly advancing multiple myeloma. In Case 4 the neurological symptoms antedated the recognition of the myeloma; in Case 5 a mild sensory neuropathy became evident three or four years after the onset of a moderately advanced form of multiple myeloma. In both Cases 4 and 5, the symptoms of neuropathy were arrested or perhaps progressing very slowly, whereas the symptoms of myeloma had visibly regressed.

The total protein level in the cerebrospinal fluid was elevated in four of our patients. It ranged from 50 to 340 mg. %, and was greatest in the patients with the most severe degrees of neuropathy. There was no obstruction to the flow of cerebrospinal fluid to explain this abnormality. Nor could the neuropathy itself be accepted as an adequate explanation, since an elevated spinal fluid protein level has been described in patients with multiple myeloma and without neurological complications (Degenhardt and Sheehan, 1949; Madonick and Solomon, 1953). The latter authors stated that there was no consistent relationship between the serum proteins and cerebrospinal fluid proteins. Their conclusions were based on estimates of total proteins obtained by standard fractionation methods, and did not take into account the possibility that abnormalities of globulin fractions could be present with little or no alteration of the total protein. Labhart, Schweizer, and Staub (1951), on the basis of electrophoretic studies in three patients with multiple myeloma, claimed that the changes in the cerebrospinal fluid protein fractions were simply a reflection of the abnormal serum fractions. This view was not substantiated by the study of the serum and spinal fluid electrophoretic patterns in one of our patients (Case 1). Serum electrophoresis showed an increase in the β_2 globulin component; the cerebrospinal fluid protein level was raised, but electrophoretic patterns were normal. It is apparent that more studies are necessary before an authoritative statement can be made regarding the cerebrospinal fluid protein elevation in multiple myeloma.

The pathological changes in the nervous system were similar in our three necropsied cases, varying only in degree. In none was there any evidence of compression of neural structures by myeloma or vertebral deformity. Microscopically, no plasma cells were seen in the nerves or roots. The most striking feature was the degeneration of the peripheral nerves, and to a lesser extent of the anterior and posterior roots, always more in the distal segments than in the proximal ones. Both the myelin sheaths and the axis cylinders were destroyed, the former more than the latter. There were also segments which showed a loss of myelin and bared axis cylinders, the segmental demyelination of Gombault. Only a moderate number of dorsal root ganglion cells were lost, even in cases in which the posterior roots and posterior columns of the spinal cord had degenerated. The alteration of anterior horn cells was most likely secondary to the axis cylinder damage in the anterior roots and peripheral nerves. The thickening of blood vessels was probably a reactive change; it could hardly be responsible for the neural changes.

Despite a careful survey of our pathological material, no amyloid was seen in the endoneurium or contiguous blood vessels. This was surprising, in view of the high incidence of amyloid in cases of myeloma and the fact that the amyloidosis complicating myeloma tends to be of the "primary" type, that is, of the type that is located in the heart, gastro-intestinal tract, and blood vessels. It has been estimated by Bayrd and Bennett (1950) that multiple myeloma is attended by primary amyloidosis in about 15% of instances. Large series of cases have been reported by Atkinson (1937), Lichtenstein and Jaffe (1947), Dahlin and Dockerty (1950), and by Snapper (1952) and Snapper *et al.* (1953). However, in none of these reports is affection of the peripheral nerves mentioned, either clinically or at necropsy. In Cases 8 and 14 of Madonick and Solomon (1953), there was said to be amyloid of the tongue and generalized amyloidosis respectively. These cases were also said to have neuropathy, but

no further statement was made regarding the relationship of the amyloidosis and the neuropathy. The case from the Massachusetts General Hospital, cited by Clarke (1956), was undoubtedly an instance of multiple myeloma with primary amyloidosis; however, it is not at all certain clinically that the patient suffered from neuropathy, and at necropsy the peripheral nerves that were examined appeared normal.

Involvement of the peripheral nervous system by amyloidosis is rare but well documented. Some authors (Kernohan and Woltman, 1942) regard the neuropathy as secondary to amyloidosis of small vessels; others (deNavasquez and Treble, 1938; Findley and Adams, 1948; Ritama and Björkesten, 1954) describe actual involvement of the nerve trunks and perineurial connective tissue by amyloid. Under any circumstance, none of the described cases of amyloid neuropathy were associated with multiple myeloma. The idea that amyloidosis is responsible for myelomatous neuropathy, though theoretically entertaining, lacks pathological confirmation.

No other explanation for the neuropathy has suggested itself. Under-nutrition was not a factor in the commonly accepted sense. All our patients appeared adequately nourished at the outset of the neurological illness, and all received large amounts of vitamins without the symptoms being affected. Two patients (Cases 4 and 5) were treated for long periods with urethane, but in neither case was there a discernible relationship between the drug therapy and the neurological symptoms. In Case 4 the symptoms of neuropathy antedated treatment; in Case 5 the neuropathy developed several years after cessation of urethane therapy. Furthermore, polyneuropathy has not been reported as a complication of urethane therapy despite the many cases in which it has been used in leukaemia and lymphoma. For the same reasons it would be unlikely that cortisone (Case 1) and stilbamidine (Case 4) were causally related to the polyneuropathy.

Any discussion of neuropathy with neoplasia brings to mind the carcinomatous variety delineated in a series of papers by Denny-Brown (1948), Lennox and Prichard (1950), Elkington (1952), Kremer and Pratt (1952), Dodgson and Hoffman (1953), Henson, Russell, and Wilkinson (1954), and Heathfield and Williams (1954). From these writings we learn that most of the patients had carcinoma of the lung, a few of other organs. The neuropathy may be predominantly sensory or motor, or mixed sensory-motor in type. The main affection is of the limbs, in a distal symmetrical distribution, but occasionally the trunk and face may also be involved. The neuropathy may have an insidious onset and steady progression, or it may evolve in a subacute manner and then undergo spontaneous arrest or remission for several months to a year or longer. The symptoms of neuropathy and of carcinoma may evolve together, but more often the neuropathy is recognized earlier. There is frequently a striking lack of parallelism in the severity of the neuropathy and the extent of the carcinomatosis; in some instances the neuropathy may represent the entire clinical picture, the carcinoma only being discovered at necropsy. Remissions in the symptoms of neuropathy are frequent and seem to be independent of any treatment undertaken for the carcinoma. Usually the cerebrospinal fluid protein level is raised, and rarely there may be a slight lymphocytic pleocytosis.

It will be readily discerned that in this description of carcinomatous neuropathy are embodied the main clinical features of the neuropathy encountered in our patients with multiple myeloma. Of special importance is the fact that the neurological symptoms may precede or entirely dominate the neoplastic ones, so that in patients with obscure neuropathies a careful search should be made for carcinoma and multiple myeloma.

Pathologically, the analogy between the neuropathy of carcinoma and of multiple myeloma is less striking. This is particularly so in relation to sensory carcinomatous neuropathy, in which degeneration of dorsal root ganglion cells is the most prominent change. In the mixed sensory-motor type of carcinomatous neuropathy, however, the pathological changes cannot be distinguished from those of myelomatous neuropathy. The various other neuropathological changes that have been described in carcinoma, such as cerebellar degeneration, myopathy, and primary degeneration of the spinocerebellar and pyramidal tracts, were not encountered in our material.

Inasmuch as carcinoma accompanied by neuropathy in the absence of secondary deposits in the nerves is loosely referred to as carcinomatous neuropathy, it might be appropriate to refer to the condition we are describing as myelomatous neuropathy. It would appear that in both of these neoplastic states some toxic or metabolic abnormality is created in the peripheral nervous system, but the mechanism remains as obscure as that of neoplasm itself.

Summary

Multiple myeloma may be associated with a polyneuropathy which does not depend on compression of nervous structures by tumour tissue. The clinical findings in five such cases are presented; in three of these post-mortem examinations were performed.

The polyneuropathy, although varying in severity, took a characteristic form in four patients. Essentially, it was a symmetrical, atrophic, areflexic, sensorimotor affection of the legs, and in two cases of the arms. The fifth patient presented a mild sensory polyneuropathy. The cerebrospinal fluid protein level was raised in four patients. In three patients the symptoms of polyneuropathy preceded those of the multiple myeloma and completely dominated the clinical picture. In two patients there was a prolonged remission of both the neuropathy and the myeloma.

The neuropathy of multiple myeloma bears a close resemblance to that of carcinoma, of the type unrelated to direct involvement by neoplasm. It is emphasized that in patients with obscure neuropathies, a careful search for both carcinoma and multiple myeloma should be made.

Pathologically, there was no evidence of compression of neural structures by myeloma or by vertebral deformity. Microscopically, no plasma cells were seen in the nerves or roots. The most striking feature was the degeneration of the peripheral nerves, and to a lesser extent of the anterior and posterior roots, always more in the distal segments than in the proximal ones. Both the myelin sheaths and the axis cylinders were destroyed. the former more than the latter. Relatively few dorsal root ganglion cells were lost. No amyloid was seen in the endoneurium or in the contiguous blood vessels.

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THE RELAPSING COURSE OF CERTAIN MENINGIOMAS IN RELATION TO PREGNANCY AND MENSTRUATION*

BY

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Intracranial tumours not uncommonly show their first symptoms, or a rapid increase in their symptoms, during a pregnancy. This occurs more frequently than can be regarded as purely coincidental, and applies to all types of tumour—extrinsic and intrinsic. On questioning a number of medical men it was evident that a popular belief is held that tumours of the pituitary are particularly likely to behave in this manner, but this contrasts with the experience of most neurologists and neurosurgeons who, similarly questioned, would instance meningiomas, angiomas, and occasionally neurofibromas.

It is not widely appreciated, however, that such symptoms may show complete remission following delivery, or, that in the case of certain slowly growing tumours, this sequence of events may recur repeatedly over a very long period, giving rise to considerable confusion in diagnosis.

Two striking cases have come under our care at the Midland Centre for Neurosurgery within a few months of each other, in each of which the type and position of the tumour was almost identical. These are recorded below and on extending this study to include other published reports of confirmed intracranial tumours showing repeated relapses and remissions during and after pregnancy, there is found a remarkable uniformity in the clinical picture, the histology, and the site of growth of the tumour.

Case Reports

Case 1.—A 45-year-old woman was referred complaining of impaired vision in the right eye. Sixteen years earlier, three weeks before the end of her fifth pregnancy, she had developed, quite painlessly, over a period of about three days, complete ptosis of the right eyelid and impaired movement of that eye. This remained until four weeks after delivery and then recovered completely. Five years later, a few weeks before the end of her sixth pregnancy, she again developed right-sided ptosis and partial oculomotor paresis, and again this recovered completely after delivery. Four years later still, three weeks before the end of her seventh pregnancy, exactly the same thing occurred, but recovery after delivery was only partial, and though the ptosis disappeared, she continued to have varying diplopia over the next eight years. During these years the ptosis frequently became complete again three days before menstruation was due and recovered during the week of menstruation. In the last 12 months her vision had begun to fail steadily and it was this that brought her under our care. The whole 16-year course had been completely painless.

Examination revealed that vision in the right eye was reduced to finger counting as a result of a large centrocaecal scotoma, and there was papilloedema in that eye. There was a partial right third nerve paresis, with total loss of upward ocular movement, but no other abnormal neurological signs.

Radiographs of the skull showed a thickening of the inner end of the right sphenoidal wing and there was a marked difference in the bone density surrounding the optic canals. A diagnosis of sphenoidal wing meningioma was made and a right carotid arteriogram carried out which did not show any definite tumour vascularity, but the carotid artery was most severely constricted intracranially over several millimetres (Fig. 1).

FIG. 1.—Enlargement of an arteriogram of Case 1 showing gross constriction of the carotid artery in its intracranial course.

*From a paper read to the Association of British Neurologists at Belfast, April, 1957.

At exploration a meningioma-en-plaque was discovered extending over the sphenoidal wing, encircling the optic nerve, and there was a tongue of tumour extending backwards to encircle and constrict the carotid artery. As much tumour as could be seen was removed and the optic nerve and the carotid artery were freed; a course of deep *x*-ray therapy was given, and two and a half years later the patient is symptom free, there is no papilloedema, and vision is better than 6/24 in that eye.

Case 2.—A 37-year-old woman in the 36th week of her third pregnancy had experienced diplopia for four weeks and numbness over the right side of the face for two weeks. Her first attacks of diplopia, 14 years earlier, had many times occurred in the pre-menstrual week and recovered during the period of menstruation. In the intervening years she had had two previous pregnancies, and in each of these, a few weeks before she was due for delivery, she had developed severe diplopia, which had recovered completely within four weeks after parturition. Her present attack was the worst, and this was the first time she had experienced numbness of the face. The course of the disease had been entirely painless.

On examination there was a mild right-sided exophthalmos and paralysis of the right third nerve. Sensation to pain was lost over the first and second divisions of the fifth nerve and impaired over the third division. Radiographs of the skull showed thickening of the inner end of the sphenoidal wing on the right and the bone surrounding the optic canal was thickened on that side.

Her pregnancy was allowed to proceed to term, and after delivery the sensory loss practically disappeared and the diplopia considerably improved.

A carotid arteriogram, six weeks after delivery, again showed little if any tumour circulation, but a curious, fusiform constriction of the intracranial portion of the artery (Fig. 2).

On exploration, a meningioma-en-plaque was found to spread over the sphenoidal wing and a thin layer of tumour extended backwards, compressing the carotid artery, and extending into Meckel's cave. The tumour was widely excised and the carotid artery freed. Following operation, the patient has a permanent ptosis and strabismus, which are being corrected by plastic procedures. She has otherwise remained well for two years.

FIG. 2.—Enlargement of an arteriogram of Case 2 showing fusiform narrowing of the carotid syphen.

Discussion

Though study of the literature reveals many reports and references regarding all types of intracranial tumour whose growth appears to have been stimulated by pregnancy, when one extracts those cases in which symptoms have completely recovered after delivery, and, in particular, those in which this sequence of events has been repeated in two or more pregnancies, a very different picture emerges.

Fischer in 1931 described a woman who developed failing vision in her first pregnancy. Vision recovered completely after delivery, but progressed again to total blindness in the seventh month of a subsequent pregnancy, again completely recovering after delivery. In 1935 he reported further on the same patient, who by that time had been discovered to have a parasellar meningioma. Hagedoorn (1937), discussing relapsing visual field changes of unknown cause during pregnancy, mentions a 36-year-old woman who developed a central scotoma in the right eye in the fifth month of her tenth pregnancy, which recovered completely after delivery, but recurred at the same stage of the next pregnancy. This was terminated and vision again recovered. It later deteriorated and she was found to have a large suprasellar meningioma. Walsh (1947) includes a case in which a central scotoma developed towards the end of a third pregnancy, recovered after delivery, and recurred two years later, when a meningioma was excised from the inner third of the sphenoidal wing. Rand and Andler (1950) described a patient who developed ptosis, exophthalmos, and visual failure towards the end of each of two pregnancies with recovery after delivery and later was found to have a sphenoidal wing meningioma. Finally, Weyand, MacCarty, and Wilson (1951), discussing the influence of pregnancy on meningiomas around the optic chiasma, include five cases showing two or more relapses and recoveries during and after pregnancy, each of which was found to have a suprasellar meningioma. They stress the fact that the symptoms developed in the later months. One of their cases also had attacks of blurred vision preceding menstruation, as in our cases.

Including our cases there are, therefore, on record 11 examples of meningiomas showing development and complete remission of symptoms during and after two or more pregnancies, and in each case the meningioma has been described as suprasellar, para-

sellar, or medial sphenoidal wing. In every case it has been notable that headache or supra-orbital pain has been minimal or absent and that the symptoms have developed during the last four months of pregnancy. As the symptoms have been central scotomata, diplopia, or unilateral ptosis, it is not difficult to imagine that disseminated sclerosis has often been diagnosed and myasthenia gravis or even aneurysms have been considered.

Explanations of varied complexity have been offered for this sequence of events, ranging from the view that parasellar tumours might be particularly sensitive to hormonal influences, to a very much more simple suggestion of a purely mechanical nature, and it is this that seems most likely. Accepting the fact that any meningiomas may increase in size during pregnancy, the particularly intimate relationship borne by these tumours to the optic and oculomotor nerves is such that only a small increase in size is required to produce quite a dramatic increase in symptoms. It is notable that spinal tumours may behave in a similar manner, room for expansion again being limited. In contrast, convexity meningiomas may enlarge considerably without any striking new manifestations.

Again, various explanations have been offered for the actual increase in size that takes place during pregnancy, but the most likely is that, as a part of the general water retention in the body, the fluid content of the tumours is increased. Some support is given to this hypothesis by Weyand, MacCarty, and Wilson (1951), who twice removed meningiomas during the course of one of the pregnancies in which there had been symptomatic relapse, and the cytology was rather different from that usually seen. The cells were markedly swollen and the cytoplasm had a curious foamy appearance, but there was no increase in the degree of cellularity or in mitotic figures. The tumours appeared to be swollen, but the cells were not multiplying, so that a reduction in size at a later date could be quite easily understood.

As a result of this study, we wish to suggest that if a patient develops unilateral scotomata or oculomotor defects during the latter half of pregnancy, particular attention should be paid to the possibility that she is harbouring a sphenoidal wing, parasellar, or suprasellar meningioma; that such a patient should be carefully investigated with this in mind and that if these investigations give the slightest suggestion that such a tumour is present, the area should be explored. This is neither a difficult nor a dangerous procedure and not only may the vision of an eye be saved if the diagnosis is established during an early relapse (a result often not achieved later, even after successful removal of the tumour), but also complete carotid strangulation, which in our cases was imminent, may be prevented. Hemiplegia may thus be avoided, even if radical removal of the tumour results in severe damage to the oculomotor nerve.

Summary

Meningiomas in the parasellar situation may produce relapse and remission of symptoms in relation to pregnancy and the menses over many years. Such symptoms—painless unilateral scotomata or oculomotor palsies—can cause serious diagnostic errors.

Two illustrative cases are described and nine others have been previously reported. The explanation of this behaviour is considered and the importance of early exploration stressed.

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A CASE OF INTRAMEDULLARY NEURINOMA

BY

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Neurinomas are among the commonest extramedullary space-occupying lesions encountered in the spinal canal. The occurrence of such neoplasms in an intramedullary site, however, is rare and raises interesting questions regarding its mode of origin. For this reason the following instance of intramedullary neurinoma is recorded.

Case Report

K., a 35-year-old farmer (N.S. 350), was admitted to the Neurosurgical Unit, Government General Hospital, Madras, India, in 1951, for inability to move the lower limbs. The onset of his illness dated back to about nine months before admission when he noticed weakness, together with a heavy feeling of the lower limbs progressing to loss of sensation. Both these symptoms progressed so he sought medical advice. He also had difficulty in emptying his bladder completely.

Physical examination disclosed that the pertinent findings were restricted to the nervous system. There were no voluntary movements in both lower limbs which were spastic and held in extension. Involuntary movements were not present and there was no muscular wasting. Examination of sensation disclosed a complete loss of appreciation of all modalities of sensation below the level of the xiphisternum. About the xiphisternum and up to about the level of the fourth dorsal dermatome there was a suggestion of dissociated sensory involvement with sparing of touch and loss of temperature and pain sensations. The knee and ankle jerks were exaggerated. An extensor type of plantar response was elicited on both sides. The patient had overflow incontinence of urine. The rest of the neurological and systemic examination was normal.

Routine laboratory investigations disclosed no abnormal findings. A cisternal myelogram showed a complete arrest of "lipiodol" at the level of the second dorsal vertebra. A laminectomy was done and the only abnormality was a fusiform enlargement of the spinal cord. An incision along the posterior midline disclosed a fairly well encapsulated tumour that was removed from the substance of the cord without much difficulty. The tumour was about 1 cm. long and ¾ cm. in diameter and tended to be more in the left than in the right half of the cord.

Convalescence from surgery was uneventful and in about three months the patient had recovered sufficiently to be able to work eight to 10 hours a day on his farm. However, the loss of pain and temperature sensations between the fourth and the sixth dorsal dermatomes persisted. Four years later, in March, 1955, the patient experienced pain in the front of the chest on coughing and a heavy feeling in the lower limbs. The latter progressed to difficulty in walking and he was admitted on June 30, 1955, with weakness of the lower limbs, more marked on the left.

Neurological examination revealed that the cranial nerves and upper limbs were normal. Both the lower limbs were spastic, the left more than the right. Power was markedly diminished on the left and moderately so on the right side. The muscles were not wasted and involuntary movements were absent. Examination of the deep tendon reflexes revealed that the knee and ankle jerks were markedly exaggerated on the left and brisk on the right side, with ankle clonus on the left. The abdominal skin reflexes were absent on both sides and an extensor type of plantar response was obtained bilaterally. Examination of the sensory system disclosed bilateral absence of pain, temperature, and touch sensations between the levels of the fourth and sixth dorsal dermatomes with retention of pressure and vibration sensations. Between the sixth and twelfth dorsal dermatomes all sensations were lost on the right and retained on the left side. Below this level all sensation was completely lost bilaterally. As on the previous admission the patient had an overflow incontinence of urine.

On lumbar puncture, the cerebrospinal fluid contained 160 mg. protein per 100 ml. There were no cells. Cisternal myelography showed that the dye was arrested at the level of the second dorsal vertebra, which was at the same level as the previous block. The old laminectomy was therefore re-opened and the lamina of one vertebra above was nibbled to ensure adequate dissection of the extradural tissues and separation of the dura. The dura was tense and upon incision the cord was found to be enlarged and tense. The latter was incised as before and a well-encapsulated tumour, 1 cm. in length and about ½ cm. in diameter, extruded and was removed with ease. Convalesence from surgery was uneventful though slower than before and about six months after operation the patient has shown signs of improvement in that he is able to walk with the aid of a stick.

Pathological Findings

The tumour removed at the first operation appeared knobbed and was about 1 cm. by ¾ cm. On section it was yellowish-white, moderately vascular, and showed tiny foci of degeneration. Histological examination disclosed

FIG. 1.—High-power view to indicate the type of cell of the tumour. Note the mitotic figure in the centre of the field. Haematoxylin and eosin.

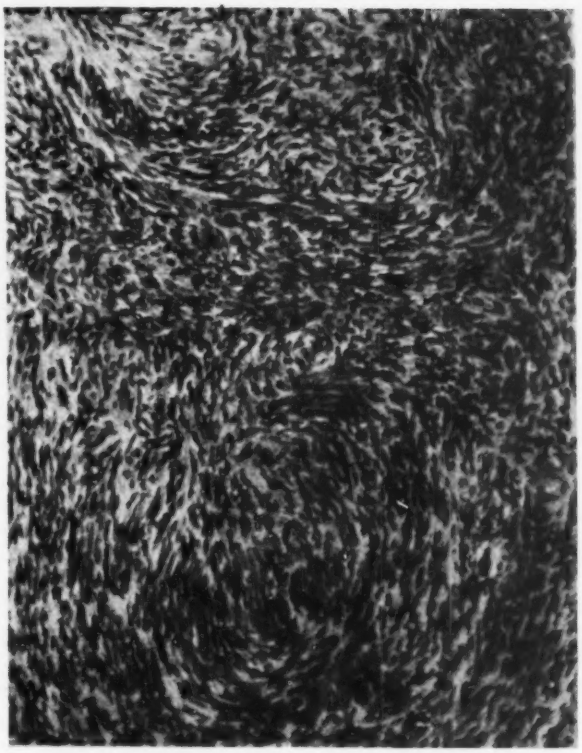

FIG. 2.—Low-power view of the tumour indicating general pattern of the architecture. Haematoxylin and eosin.

interlacing bundles of elongated cells. The cytoplasmic outlines were indefinite and appeared to consist of long, slender fibres running along the long axis of the nuclei. The nuclei were oval or elongated, occasionally curved, and were either vesicular with a well-defined chromatin network or pyknotic. The nuclei were arranged occasionally in palisades but more often in whorl-like formation. Mitoses were absent in the first specimen but a careful search of the second revealed a few mitotic figures. The cytoplasmic fibres were not stained by Mallory's phosphotungstic acid haematoxylin. They, however, were well stained by methods for demonstrating collagen and were impregnated with ease by silver methods for reticulum.

On reviewing the clinical features presented by this case it becomes apparent that the symptoms were those of a slowly growing intramedullary space-occupying lesion. The absence of any definite root pains at the onset of his illness and the subsequent course, which resulted in the picture of an incomplete transection of the spinal cord in as short a period as nine months, were highly suggestive. Support for this contention was afforded by the presence of dissociated sensory loss demonstrable over the dermatomes innervated by the fourth to sixth dorsal nerves. It was therefore not surprising that laminectomy revealed an intramedullary lesion. The rapid functional recovery after surgery could only mean that any lasting damage to the parenchyma of the cord must have been minimal, most of the symptoms being attributable to pressure or displacement.

The return of the patient's symptoms was the result of recurrent growth of the tumour, and the incomplete Brown-Séquard syndrome that he presented could be explained by the fact that the growth was eccentric, being located more to the left in the cord. It is also not surprising that recovery from the second operation was not as quick or as effective as on the previous occasion.

The histopathological findings were, however, quite surprising. The typical cell, as also the architectural features of this tumour, were those of a neurinoma. The absence of any glial fibres, as also the abundant reticulum in the tumour, rule out, in our opinion, the possibility of it being an astrocytoma (polar spongioblastoma), some of which in the cord have been wrongly labelled " centralneurinoma ". The ease with which the tumour was delivered from the cord also adds support to our contention, for it indicates that there was no infiltration into the adjacent neural parenchyma such as has been demonstrated to be the classical behaviour of

even the most "benign" astrocytomas (Scherer, 1940)

Discussion

The rarity of recorded instances of true intramedullary neurinomas is evident from a review of the literature. Rasmussen, Kernohan, and Adson (1940) encountered a solitary instance of intramedullary neurofibroma in a series of 557 spinal tumours. This tumour, which was mentioned later by Woltman, Kernohan, Adson, and Craig (1951), was encountered in a 12-year-old boy who complained of pain and weakness of the limbs for about four years before coming under observation. The tumour was found in the cervical cord between the levels C4-C7. There was some neurological improvement after surgery, but the ultimate fate of the patient is not known. Pathological examination revealed a neurofibroma.

A case of "intramedullary neurinoma" was reported by Roka in 1951 but no details are available.

A third case that we have recently come across only by title was the one presented by Riggs and Clary (1957) at the annual meeting of the American Association of Neuropathologists in June, 1956. The title of this paper, "A Case of Intramedullary Sheath Cell Tumour of the Spinal Cord: Consideration of Vascular Nerves as a Potential Source of Origin", indicates the views of these authors regarding the origin of that tumour in its unusual site.

The histogenesis of neurinomas has been a point of dispute, with opposing schools putting forward their own points of view. Mallory (1920), Penfield (1927), and others, for example, Tarlov (1940), on the basis of staining methods believe that these tumours arise from the connective tissue of the nerve sheath and as such are fibroblastic in nature. Masson (1932), on the contrary, contended that neurinomas arise from the Schwann cells and are thus ectodermal in origin. This view appears to be supported by the observations of Murray and Stout (1940) who also offer an explanation for the connective tissue content of these tumours.

The occurrence of a nerve-sheath tumour primarily in an intramedullary site as in the present case is unique enough to call for an explanation. Kernohan (1941) believes that an intramedullary neurinoma (neurofibroma) may arise from a small nerve bundle that enters the spinal cord in company with a perforating blood vessel. Riggs and Clary (1957) appear to propound a similar view in reporting their case. While the study of the present case can neither confirm nor deny their views, it is difficult to understand why if this view is correct intramedullary nerve-sheath tumours are so rare.

An alternative explanation that, in our opinion, could also account for the rarity of such neoplasms is that they arise from neural crest cells that could possibly have been displaced into the developing spinal cord early in embryonic life. According to most authors the cells of the Schwannian sheath along with a number of other structures are derived from the neural crest (Hamilton, Boyd, and Mossman, 1945). It might be recalled that with the formation of the neural groove the cells on either side of the summit undergo differentiation and come to lie on either side of the newly-formed neural tube. As this differentiation occurs at or about the same time as the closure of the tube it is possible that very rarely a few of these cells could be displaced and enveloped in this structure. Neoplastic transformation of these cells could later result in a neurinoma. That a phenomenon such as this is not unique to such cells is amply demonstrated by the occurrence of other neoplasms, such as dermoids and epidermoids and adamantinomata of the pituitary, that are known to arise from such ectopic cell rests. It is also possible, as has been contended by Horwitz (1941) in the case of chordomas, that such ectopic cell rests undergo neoplastic transformation more readily than primitive cells of a similar type that survive in their normal sites. Admittedly there are many more factors determining neoplasia than the mere presence of such cell rests in an ectopic site, and this fact, together with the possible rarity of such ectopic displacement in the spinal cord, could in our opinion amply account for the extreme rarity of intramedullary neurinomas.

Summary

A case is recorded of a recurrent intramedullary neurinoma in a 35-year-old male.

The possible mode of origin of a neurinoma in such an unusual site is briefly discussed.

Our thanks are due to the Dean, General Hospital, Madras, for permission to publish this article and to Professor G. S. Viswanathan, Professor of Pathology, Madras Medical College.

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RECURRENT MULTIPLE CRANIAL NERVE PALSIES

BY

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The material for this paper comprises four case reports, which must necessarily be presented in some detail, having regard to the points in which they resemble and differ from one another. The resemblance between these cases is close enough to suggest that they constitute a recognizable clinical syndrome. As to their aetiology, the data permit no definite conclusion but suggest the possibility of a hypersensitivity reaction as a common factor.

Case Reports

Case 1.—Mr. S., aged 31, was first seen on June 29, 1951, complaining of headache and double vision.

There was no relevant family history. The past history revealed that while serving at sea in 1942 he had a facial paralysis of sudden onset, he could not recollect on which side. The onset was not accompanied by pain, paraesthesiae, or other symptoms. Recovery was complete in three weeks. In October, 1945, again while at sea, he noticed double vision. At this time he was sleeping badly and felt generally unwell, but not feverish. He was admitted to hospital at Haifa on October 10, 1945, and from the notes made at that time the following particulars are available. He complained of headache and slight pyrexia. There was paralysis of the right sixth cranial nerve. The cerebrospinal fluid was under a pressure of 190 mm. It contained 2 lymphocytes per c.mm., 30 mg. per 100 ml. of protein, 740 mg. of chloride, and no excess of globulin. The Wassermann reaction was negative. The white blood count was 7,200 with a normal differential count. The Kahn reaction in the blood was negative. The ocular paralysis had recovered by October 16. He had a fortnight's convalescence and returned to full duty.

In March, 1946, he was demobilized A.1, but afterwards felt vaguely unwell and tired easily.

In April, 1948, for a period of 10 days he suffered from vertical headache, mainly at night. Some time later headache of a similar type recurred, and he became aware of difficulty in protruding his tongue to one side, he thought to the left. These symptoms soon subsided, but he then noticed a swelling in the right side of the neck. He was seen in Inverness by Mr. Hamilton, and a biopsy was carried out and an abscess drained. The diagnosis of tuberculous adenitis was made and confirmed histologically.

In July, 1950, he again experienced vertical headache, keeping him awake at night, and at the same time inability to protrude his tongue to the left with consequent dysarthria. These symptoms cleared up in 10 days. Early in 1951 discomfort and swelling appeared in the left testis, and he was seen by Mr. Hamilton, who diagnosed a tuberculous infection.

In April, 1951, he again suffered from headache, which began in the right parieto-temporal region and was severe, especially at night. Later the pain radiated into the right lower jaw and was also experienced in the left temple, radiating into the left lower jaw. This continued for a few weeks, when he suddenly noticed double vision, and the headache ceased. The images appeared side by side and were most separated when he looked to the left. Within two weeks the diplopia subsided but might recur occasionally when he was fatigued. Early in June he again complained of double vision with vertical displacement of the image, and slight left-sided ptosis. He was admitted to hospital, where the cervical adenitis and epididymitis were unchanged. Radiological examination showed no abnormality in the skull, and no evidence of active pulmonary disease. The blood showed Hb 91%, white blood cells 7,200 per c.mm. with a normal differential count, and the blood sedimentation rate was 8 mm. in the first hour. The urine contained no abnormal constituents and was sterile on culture. Lumbar puncture yielded a clear cerebrospinal fluid at a pressure of 105 mm. of water with a prompt rise and fall on jugular compression. It contained 1 lymphocyte per c.mm., protein 30 mg., no excess of globulin, and chlorides 655 mg. per 100 ml. The colloidal gold curve showed no elevation.

Examination by the writer on June 29, 1951, revealed in addition to the right cervical adenitis and left epididymitis an incomplete left third nerve palsy. There was ptosis, with an enlarged pupil and weakness of all movements innervated by the nerve, especially elevation. No other abnormality was found in the examination of the nervous or other systems, but he looked ill. He returned home to remain under observation and early in July rather suddenly found difficulty in chewing, which he felt was due to weakness of the left jaw muscles. On palpation he discovered that the left masseter was not acting. This weakness, which was not accompanied by pain or paraesthesiae, disappeared in a few days. A week later he noticed in the morning a sense of dysequilibrium with a tendency to sway to either side. This worsened during the day, and when he lay down he found that the slightest movement caused a sensation as of objects seen revolving. This was accompanied by vomiting. There was no

tinnitus or deafness. For the next two days he experienced aggravation of the vertigo on turning his head to the left. He remained in bed 10 days, during which time the diplopia remaining from the third nerve lesion disappeared. Throughout the whole of this episode he had headache of the kind previously experienced from time to time during the course of his illness.

He was admitted to Guy's Hospital on August 15, 1951, when he had no symptoms other than general malaise. He was afebrile. No abnormality was to be found in the nervous system. In the neck a number of small, mobile, hard glands were present in the right posterior triangle, which to the feel were partly calcified. The left epididymis was enlarged, especially in its upper pole. He was examined by Dr. W. N. Mann, who confirmed these observations but could find no other abnormal physical signs. Radiographs of the skull showed no abnormality. Radiographs of the chest showed extensively calcified right cervical glands, but the lung fields were clear and the heart and hilar shadows normal. The cerebrospinal fluid was clear and colourless, with no cells, protein 30 mg. per 100 ml., no increase of globulin, and normal reduction of Fehling's solution. The Wassermann reaction was negative and the colloidal gold curve normal. The serum proteins were normal. No abnormal constituents were found in the urine, and the cultures were sterile. He was examined by Mr. F. R. Kilpatrick, who was of opinion that there had been a tuberculous focus in the left epididymis but that this organ was now practically normal. There was no clinical evidence of any active disease of the genito-urinary tract, and intravenous pyelograms were normal. A blood count on August 17 showed that the haemoglobin was 88% and the white cells numbered 6,000, of which 70% were polymorphonuclear. The blood sedimentation rate was 10 mm. in the first hour and 38 mm. in two hours. Dr. Mann thereafter took charge of the patient, and I am indebted to him for the subsequent history.

Treatment was begun with intramuscular streptomycin and *p*-amino-salicylic acid (P.A.S.) on September 4 and continued for a period of six weeks. The blood sedimentation rates during this period were as follows:—

	1 Hour	2 Hours
Sept. 4	17 mm.	39 mm.
Sept. 17	15 mm.	37 mm.
Oct. 3	9 mm.	23 mm.
Oct. 10	7 mm.	19 mm.
Oct. 16	8 mm.	19 mm.

When examined by the writer on October 6 he felt mentally more alert and vigorous. He had had no return of headache. Until the end of September he had had occasional diplopia in the early morning but this had not occurred for a week. On examination the only abnormality found in the nervous system was that the left pupil was larger than the right. He was discharged from hospital on October 18 and advised to take three months of graduated convalescence. He was thereafter seen by Dr. Mann on February 4, 1952. He then stated that he felt extremely well and had no complaints at all. No new physical signs were found. Radiographs of the chest showed no abnormality. The blood sedimentation rate was 2 mm. in the first hour and 6 mm. in the second.

He remained well until July, 1953, when glands in the right side of the neck rapidly enlarged. After two weeks the swelling began to subside. At this juncture it is reported that the blood sedimentation rate and radiographs of the chest were normal. He was seen by Dr. Mann on July 23, who observed the right cervical glands to be larger than before, but advised that as he was now improving no further antibiotic treatment should be given at the moment.

In October, 1953, the patient complained of general malaise with slowness of thought and difficulty in concentration. He was re-admitted to Guy's Hospital under the care of Dr. Mann on November 15, 1953. Dr. Mann found fresh enlargement of the left epididymis, and possibly some extension of the enlarged right cervical glands. The blood sedimentation rate was 13 mm. in the first hour. Radiographs of the chest showed no disease of the lungs. No neurological symptoms or signs had recurred. He was treated with streptomycin, 1g. daily, which was changed to 1g. thrice weekly together with isoniazid, 300 mg. daily. This treatment was continued for a month, during which he showed rapid clinical improvement, especially in his mental state. The blood sedimentation rate on December 9 was 11 mm. in the first hour and 30 mm. in the second. On December 21 he developed a swelling in the upper pole of the right epididymis and was seen by Mr. Kilpatrick, who carried out a right epididymectomy on January 13, 1954. Histological examination confirmed the tuberculous nature of the lesion. Treatment with streptomycin and isoniazid was continued. Dr. Mann, in consultation with Sir Geoffrey Marshall, advised that the patient be transferred to the King Edward VII Sanatorium at Midhurst, where he was admitted on March 3, 1954, and discharged on September 1, 1954, having been given isoniazid and P.A.S. during the whole period of his stay. In November, 1954, the patient noticed enlargement of a gland in the right side of his neck and was again seen by Dr. Mann, who observed swelling of a gland adjacent to the group previously involved. This, however, was subsiding, and 14 days later was smaller. On January 25, 1955, it was no longer enlarged, the blood sedimentation rate was 11 mm. in the first hour, and radiographs of the chest were again normal. He reported in October, 1957, that he was in good health and had remained so for over two years.

Case 2.—This patient was seen with Dr. Murray Baird at the Shaughnessy Hospital, Vancouver, B.C., in September, 1953. I am much indebted to him, and to the patient, who is herself a doctor, for providing me with the clinical and pathological data presented here.

Mrs. K. was aged 27 on her first admission to Shaughnessy Hospital on April 24, 1953.

In the family history the only observation of possible relevance was that a sister had tuberculous glands removed from her neck in childhood.

The patient between the ages of 16 and 19 was said to have had anaemia with low blood pressure and a liability to fainting attacks. During this period she had occasional attacks of what was called intercostal fibrositis.

At the age of 17 she began to have occasional headache at intervals of three to six weeks.

In January, 1950, she had a right facial paralysis of rapid onset diagnosed at the time as a Bell's palsy. Recovery was virtually complete in three months. In June, 1951, there was a sudden onset of diplopia found to be caused by a right sixth nerve palsy, which cleared up in two weeks. In September, 1951, she had bilateral parotitis of 10 days' duration, diagnosed as mumps. During the six months before her admission she had two bouts of continuous headache lasting several days. A third bout had preceded her admission for a fortnight. It was described as continuous day and night, waking her at night, of fronto-occipital distribution and throbbing character, and increased by stooping, bowel movement, and coughing. On the day before admission she felt feverish and ill with nausea and aching in the jaws. On admission her temperature was 100° F. but fell to normal two days later. No abnormal physical signs were found at this stage. On May 2 she developed right-sided headache with pain in and behind the right eye, and complained of diplopia, and in the course of the next two days developed an incomplete right third nerve palsy. At this stage she was examined by Dr. R. B. Kerr, who found the liver palpable at one inch below the costal margin and the spleen palpable at the costal margin. On May 6 lumbar puncture was done and a pressure of 165 mm. recorded. The fluid was clear and contained 3 lymphocytes per c.mm. and 25 mg. per 100 ml. of protein.

Radiographs of the chest showed a small calcareous scar in the right mid lung field and a small calcified gland in the right hilar area. Radiographs of the skull, nasal sinuses, and teeth showed no abnormality. The blood sedimentation rate (Westergren) was 35 on admission and remained high throughout her stay in hospital, being 43 on May 19. The white and red blood counts and blood films showed no abnormality. The Paul-Bunnell test was negative as also was the agglutination test for *Brucella abortus*. No abnormality was found in the urine. The serum proteins were normal. During her stay in hospital her general symptoms improved, as also the third nerve palsy, but when discharged on May 20 she still had diplopia.

She was readmitted on June 3 with a two-day history of headache, vertigo, and vomiting. These symptoms subsided in the course of three days, leaving her for a further week with a liability to vertigo on quick movement of the head. On admission she was recorded to have a slight degree of right third nerve weakness. The liver and spleen were still palpable. She was afebrile, but the blood sedimentation rate was 47. The blood count and films showed no abnormalities and the serum proteins were again normal. Radiographs of the chest showed no change and radiographs of the hands and feet showed no abnormalities. Two weeks after this second admission several subcutaneous nodules were observed on the legs. These are described by the patient as having been about the size of an almond and slightly tender, the overlying skin being red for the first 24 hours. Altogether about 14 nodules were noted. Two of these were removed for histological examination by Dr. M. V. Rae. They showed granulomatous tissue containing large numbers of multinucleated giant cells with no necrosis or caseation.

Dr. Rae's opinion was that the biopsy did not support the diagnosis of periarteritis nodosa, which had at one time been suggested. He thought the picture suggestive of Weber-Christian's panniculitis but that sarcoidosis was an alternative possibility.

Dr. Baird has kindly sent me sections of this material which have been submitted to Dr. Navasquez at Guy's Hospital. His opinion is that the morphology is consistent with either Boeck's sarcoidosis or non-caseating follicular tuberculosis.

The patient was discharged on July 22, 1953, and at that time still had diplopia and complained of headache when overtired or on straining. She tired easily, and her evening temperature was generally 99·4° F. She was then given a three-month course of treatment with streptomycin and P.A.S. (The exact dose has not been ascertained.) The blood sedimentation rates (Westergren) for the first hour during this period were as follows:

July 29	44 mm.
August 21	37 mm.
August 28	43 mm.
September 15	40 mm.
September 22	44 mm.
November 9	20 mm.

At the end of this treatment the diplopia had disappeared. She still, however, tired easily and had occasional headache, and the evening temperature ranged from 99° to 100° F. Thereafter her general condition improved and she became afebrile.

In April, 1954, she developed tenderness in the left lacrimal gland with sharp stabbing pain on lacrimation. This was followed by diminished tear production on that side. Shortly after this she went to Germany, her husband being in the Canadian Army. A month later she noticed wrinkling of the scleral epithelium just lateral to the iris of the left eye with smarting and a feeling as if a foreign body were present. She consulted an ophthalmic surgeon, who told her the trouble was due to a blocked lymphatic gland and prescribed cortisone ointment.

She subsequently reported in March, 1955, that she had had a child in the previous October, that her general health was good and that she had had no further symptoms of her old illness with the exception of two further subcutaneous nodules in the past few weeks.

Case 3.—Mrs. S., aged 57, was referred by Dr. Robinson, of Ackworth, on February 28, 1955, having recently recovered from an episode of double vision.

There was no relevant family history. In her childhood she had had enlarged glands in the left side of the neck for which an operation was performed. Otherwise she had had no illness until 1950, when she felt generally ill and tired, and was said to have had some cardiac irregularity. From this she recovered with rest.

In January, 1951, she had a sudden onset of left facial paralysis without pain or paraesthesiae, and with no subjective involvement of taste. Recovery was virtually complete at the end of two weeks. Six weeks later she suddenly became aware of inability to protrude her tongue to the left. A left hypoglossal paralysis was confirmed by medical observation, and cleared up in a week.

In August, 1952, she found one morning that her vision was blurred and by the evening had diplopia with vertical displacement of the images. With this there was no headache or other symptom. Six days later she was examined by Dr. Hugh Garland, who has kindly let me refer to his observations. At the time of this examination there was no diplopia but she tended to tilt her head backwards. No other abnormal physical signs were found. From the history Dr. Garland concluded that there had been a lesion of the right third nerve. She was admitted to hospital for investigation and the cerebrospinal fluid was found normal in every respect, the Wassermann reaction being negative in fluid and blood. At the end of two weeks from the onset she no longer experienced diplopia at any time and remained well until September, 1954, when she began to feel tired and wanting to rest. After a week or two she again experienced diplopia, which disappeared in a week. At the end of December a left facial weakness appeared, which lasted only for 48 hours. On January 6, 1955, she again experienced diplopia and was seen by Dr. Garland on January 12, who found that her vision was blurred on looking downwards and to the right only, though there was no obvious squint. He observed no other abnormal physical signs. On the suspicion that she might be suffering from myasthenia gravis he prescribed prostigmin, which she took up to 45 mg. thrice daily. As this caused colic she ceased taking it after a few days. She stated that the diplopia was already improving when she started the treatment and became no worse when she ceased taking the tablets. It lasted in all for about a fortnight. In the last week of January she developed herpes zoster in the distribution of the right second, third, and fourth lumbar dermatomes.

Examined by the writer on February 28 she appeared alert and well, and no abnormal physical signs were found except a slight left lower facial weakness, the scars of the recent herpetic eruption, and a scar in the left side of the neck resulting from the operation for cervical adenitis in childhood.

In view of the experience gained from Case 1 her doctor was advised to have the possibility of an active tuberculous infection investigated. She was then seen by Dr. J. J. Danaher, consultant to the Chest Clinic, Barnsley, who has kindly supplied the following data. No clinical evidence of active tuberculosis was discovered, but tuberculin sensitivity tests at that time, and when repeated after an interval of three months, showed: To O.T. 1 in 10,000 (Mantoux) a positive severe reaction, oedema 16 mm.; erythema 22 mm.; to the P.P.D. patch test, a positive reaction; severe vesication in both bovine and human elements.

His conclusion was that she was suffering from an active, but indolent, tuberculous infection of uncertain location. She was accordingly treated on his advice with bed rest and isoniazid in a daily dosage of 330 mg. for three months. Eighteen months after the completion of treatment she was reported to be in excellent health and in her own words " better than she had felt for years ". The cranial nerve palsies had not recurred. At this time the sensitivity reaction to O.T. in a 1 in 10,000 dilution was minimal.

Case 4.—I am indebted to Dr. N. S. Alcock for the opportunity of seeing this patient and referring to his observations.

Mrs. M., a widow, aged 63 at the time of my examination in October, 1957, was then complaining of some difficulty in chewing and articulation.

In her family history the relevant facts were that her mother had suffered from asthma in her later years, and that her father had been subject to headaches like her own. She married at the age of 31 and had one child, who died of measles and pneumonia aged 7. She described herself as always nervous, but since childhood had had no particular illness until 1950. She then had a period of two to three weeks of more or less continuous mid-frontal headache and after this lost weight.

In March, 1951, similar headache recurred, she felt generally ill, and after two weeks experienced diplopia. She was subsequently seen at the National Hospital, Queen Square, by Dr. M. J. McArdle, who found paralysis of the left sixth nerve. The Wassermann reaction was negative in her blood. The haemoglobin was 100%, and the white blood count 10,000 per c.mm. The E.S.R. was 14 mm. in the first hour. The urine contained no albumin, sugar, or red cells. Radiographs of the skull, including the superior orbital fissures and optic foramina, were normal. Intermittent headache continued, but the diplopia improved and had disappeared by August. In November in the course of a week-end, during which she felt generally ill, she developed a left facial paralysis, from which recovery was complete in a month. At this time she began to have attacks of asthma. These attacks would last for an hour or so, and would occur in bouts with intervals of freedom. The liability to headache continued.

In May, 1953, she again felt generally ill and in the course of the next day or two developed diplopia, which proved due to a paralysis of the right sixth nerve. From this she recovered in three months. The asthma and headache continued, and in October of this year diplopia recurred with lateral separation of the images, but no observation is available as to which muscle was at fault. On this occasion the diplopia lasted six weeks, and there was another similar episode in August, 1954.

In February, 1956, she again had a left facial palsy of subacute onset, recovering in a month, and a further episode of diplopia in June lasting for four months. During the period 1955 to 1957 the attacks of asthma became progressively less frequent and severe, but intermittent headache continued, being now mainly in the left parietal region.

In April, 1957, she noticed difficulty in pronouncing sibilants and inability to pass food across her mouth, and when examined by Dr. Alcock was found to have paralysis of the right twelfth nerve. She was admitted to hospital under his care, where no signs of nervous disease were found other than the paralysis of the right side of the tongue. The E.S.R. was 5 mm. in the first hour, and haemoglobin 112%. The cerebrospinal fluid showed no cells, 60 mg. of protein, a negative Wassermann reaction, and a negative Lange curve. Subsequently radiographs of the skull and chest were normal.

At the time of my examination the hypoglossal palsy

was nearly recovered, and the tongue showed no wasting or fibrillation. No other abnormal signs were found in the nervous system. The blood pressure was 170 and 85 mm. Hg. The retinal arteries were a little uneven in calibre. The pulses in both carotid, temporal, dorsalis pedis, and posterior tibial arteries were normal. It was some months since her last bout of asthma, and she stated that her headaches were becoming less frequent and less severe.

Discussion

In each of the cases related there was a succession of cranial nerve palsies of rapid onset and transient duration, occurring at irregular, and sometimes long, intervals over a period of several years. For convenience of comparison the order and time intervals are summarized in Table I.

It will be noted that with the exception of vertigo in Cases 1 and 2, assumed to be due to involvement of one of the vestibular nerves, the affection was confined to motor nerves. Common to all cases was involvement of the seventh nerve, and in all but Case 4 this was the first of the series of cranial nerve palsies. In Case 2 the cranial nerves affected were all on the same side with the possible exception of the vestibular lesion presumed to have caused the episode of vertigo. The site of the lesion causing vertigo in this case and in Case 1 cannot be determined as no caloric tests were done. In Cases 1, 3, and 4 at one time or another cranial nerves on either side were affected. There was no evidence in any case of involvement of the conducting tracts in the brain stem or of any other part of the nervous system. Headache was a prominent symptom in Cases 1, 2, and 4, but was absent in Case 3. In Case 2 the aggravation by coughing and straining was suggestive of intracranial disease.

The cerebrospinal fluid in each case was normal in every respect, including a negative Wassermann reaction and normal colloidal gold curve.

From the neurological aspect these cases are like enough to one another and so different from any well recognized disease of the nervous system that they might be suspected on these grounds to have some common factor in their aetiology. That this was of a toxic or infective character appears probable, for in all four cases there were from time to time symptoms of constitutional disturbance. In Case 1 these symptoms were eventually proved to be due to a tuberculous infection of a particularly chronic kind, without pulmonary involvement, which eventually responded to antibiotic treatment. From the time this was begun there was no recurrence of the cranial nerve palsies, although evidence of active infection was still present three years later. During the subsequent three years, however, there has been no sign of further activity.

In Case 2 there was no evidence of active tuberculous infection. There were, however, several features suggestive of sarcoidosis. The appearance of subcutaneous nodules in this disease is recognized, and the biopsy findings in this case were consistent with the diagnosis. The enlargement at one time of the liver and spleen, and the later affection of a lacrimal gland, are also suggestive. So also is the chronic nature of the illness, fresh subcutaneous nodules being reported by the patient two years after her first admission to hospital for constitutional symptoms,

In Case 3 the only evidence for active tuberculous infection was that derived from skin sensitivity tests together with the diminished skin sensitivity and apparent clinical recovery after a course of treatment with isoniazid.

In Case 4 the earliest symptoms were headache and loss of weight, and the first episode of cranial nerve palsy and several subsequent episodes were preceded by a period of general malaise. Within a year of the first symptoms asthma developed and continued thereafter for five years.

Cranial nerve palsies are not known to occur in the course of tuberculous infection apart from tuberculous meningitis, and it is evident both from clinical observation and the examination of the cerebrospinal fluid in these cases that this cannot have been present.

Cranial nerve palsies, however, have been frequently reported in sarcoidosis (Colover, 1948; Jefferson, 1957). Any of the cranial nerves may be

TABLE I

ORDER AND TIME INTERVALS OF CRANIAL NERVE PALSIES IN PRESENT SERIES

Case 1		Case 2		Case 3		Case 4	
Cranial Nerve Affected	Date	Cranial Nerve Affected	Date	Cranial Nerve Affected	Date	Cranial Nerve Affected	Date
7 ? R or L	1942	7 R	1950, January	7 L	1951, January	6 L	1951, March
6 R	1945, October	6 R	1951, June	12 L	1951, March	7 L	1951, November
12 ? L	1948, May	3 R	1953, April	3 R	1952, August	6 R	1953, May
12 L	1950, July	8 Vestibular	1953, June	3 (Probable)	1954, September	Diplopia	1953, October
6 L	1951, April			7 L	1954, December	Diplopia	1954, August
3 L	1951, June			3 (Probable)	1955, January	7 L	1956, February
5 Motor L	1951, July					Diplopia	1956, June
8 Vestibular	1951, July					12 R	1957, April

affected. The facial nerve is that most frequently involved, and this may occur in the absence of parotitis. These cranial nerve palsies are often transient. They are presumably due to sarcoid nodules involving the sheath of the nerve or neighbouring meninges. Meningeal involvement may cause headache, and sometimes obstructive hydrocephalus (Colover, 1948). Headache was a prominent symptom in Cases 1, 2, and 3 of the present paper, and in Case 2 was of hydrocephalic type. There is, however, no case known to the writer in which a history of recurrent, transient cranial nerve palsies over a period of several years has been recorded in association with an established diagnosis of sarcoidosis. Nor was there anything to support the diagnosis of sarcoidosis in the other cases recorded here.

The aetiology of sarcoidosis remains uncertain. Coope (1952), summarizing the evidence at that time, concluded that in most cases the sarcoid lesion was an atypical proliferative reaction to the tubercle bacillus or to some chemical constituent of that organism. Evidence in favour of Coope's hypothesis has been presented by Nethercott and Strawbridge (1956), who found in sarcoid lesions chemical substances which are believed to be derived from tubercle bacilli, concluding that these lesions had previously been tuberculous, though there was no clinical or bacteriological evidence of tuberculous infection. Yet the association of tuberculosis and sarcoidosis is inconstant, and it appears at present best to regard sarcoidosis as a disease only in the sense that it has recognizable clinical and histological features (*Lancet*, 1956) with the qualification that in some cases tuberculous infection may be a causal factor. Jefferson (1957) has lately reviewed the problem and inclines to the view that sarcoidosis is not an aetiologically pure condition but represents a non-specific tissue reaction of the hypersensitivity type.

To return to the cases presented in this paper, they appear to represent a homogeneous group within the syndrome of polyneuritis cranialis. In one instance the clinical diagnosis of sarcoidosis appears tenable, and in another active tuberculous infection was present. Of the two remaining cases, in one there was some evidence in favour of tuberculous infection, and in the other an association with asthma. It seems possible, therefore, that these recurrent cranial nerve palsies may represent a selective hypersensitivity reaction involving the connective tissue elements of the nerves or their meningeal coverings, which is not specific for any single cause. In this respect the syndrome would resemble sarcoidosis, in which disease transient cranial nerve palsies are known to occur.

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FINGER TREMOR IN TABETIC PATIENTS AND ITS BEARING ON THE MECHANISM PRODUCING THE RHYTHM OF PHYSIOLOGICAL TREMOR

BY

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In a recent paper, Marshall and Walsh (1956) have considered various possible explanations of the tremor with a characteristic peak frequency of 8 to 10 c./sec. which is associated with muscular contraction in healthy subjects. Among other theories, they consider but reject the hypothesis that tremor may be due to oscillation round the "servo-loop" from muscle spindle to muscle (Halliday and Redfearn, 1956; Hammond, Merton, and Sutton, 1956). Three reasons are given for rejecting this hypothesis: (1) The similarity of the frequency of tremor in muscles having short neural pathways to the cord with that in muscles of the distal parts of the extremities; (2) the fact, reported by them, that young children show a tremor rhythm of low frequency, whereas reflex time increases with growth and might be expected to produce a slower rhythm as it did so; (3) evidence which is taken to show that tremor persists following deafferentation.

The present paper is concerned with the third of these reasons. Under this heading, two authorities are cited (Lashley, 1917; Altenburger, 1937), but neither appears to offer sufficiently good grounds for settling the matter one way or the other. Lashley's paper deals not with a deafferented limb but with a leg rendered anaesthetic from the knee downwards following an injury to the cord at a higher level. It is true that in this case the knee jerks were absent, and this might appear to indicate additional damage to the reflex arc, but, as Kuhn (1951) has pointed out, permanent arreflexia is a not uncommon sequel to spinal transection at a higher level. It cannot therefore be regarded as conclusive evidence of damage to the reflex arc itself. The relevance of the clinical assessment of the tendon jerk to the activity of the stretch reflex will be considered further in the discussion. In any case, Lashley only mentions the 10 c./sec. rhythm in a single sentence at the end of his paper. Altenburger's recordings of arm movements in a subject with posterior rhizotomy were made with a mechanical system and it is by no means clear that the record does show the 10 c./sec. rhythm.

The present paper presents the results of recording and analysing the frequencies of finger tremor in eight patients suffering varying degrees of deafferentation due to tabes dorsalis. It will be shown that the tabetic patients can be divided into two groups, those without a 10 c./sec. rhythm and those with an increased rhythm, and that the absence of the rhythm is very clearly correlated with the degree of deafferentation as determined by clinical testing. In the case of the less severely deafferented tabetic patients, who showed an increase in the rhythm compared with healthy subjects, it will be argued that such an increase on partial deafferentation is by no means a surprising observation on the "servo-loop" hypothesis. The evidence from these patients is therefore regarded as supporting this hypothesis.

Method

Tremor was recorded photo-electrically from the right index finger, and a continuous analysis was made automatically of frequencies between 1·5 and 30 c./sec. The apparatus has been fully described elsewhere (Cooper, Halliday, and Redfearn, 1957), and the method of recording and analysis of the records was the same as for the analysis of tremor in healthy subjects (Halliday and Redfearn, 1956). The subjects were out-patients attending the National Hospital. In each case tremor was recorded for 50 seconds, first with the finger unloaded and then for two further periods with a 50 or 100 g. weight strapped beneath the terminal phalanx with cellulose tape. Results are presented as force spectra for frequencies between 1·5 and 30 c./sec., calculated from an analysis of the angular velocity of the finger about the metacarpophalangeal joint.

Results

Assessment of Degree of Deafferentation.—Since the object of investigating tremor in tabetic patients

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was to determine the effect of a lesion interrupting the reflex arc, the assessment of the relative degree of deafferentation in different patients was of great importance. A full clinical examination was carried out in each case and sensory damage was assessed by the appreciation of pain (pin-prick), light touch (cotton wool), and position sense; the level of activity of the tendon jerks was also recorded. As tremor was recorded from the right index finger in each case, interest is directed towards the degree of deafferentation of the right upper limb. Sensory data are therefore presented for the right upper limbs only. In fact, however, all limbs were tested and there is little difference in the final assessment if the whole picture is taken rather than the localized one. It is not of course practicable to limit testing to the particular muscles producing finger tremor, as many muscles may be concerned and the eliciting and measurement of the tendon jerks in each of them would be difficult and laborious.

The findings are summarized in Table I, where the patients are arranged somewhat arbitrarily in what appears to be the order of decreasing deafferentation. Thus the first two patients (Nos. 1 and 2) showed severe sensory loss combined with complete absence of deep reflexes, while the last three (Nos. 6 to 8) showed little or no sensory loss together with tendon jerks which were still present and active (the actual level of activity varied and in one case (No. 6) some of the jerks were only elicitable on reinforcement). Between these two extremes there is a group of patients (Nos. 3 to 5) in whom the signs were more equivocal, in that absent tendon jerks were associated with minimal sensory changes (Nos. 3 and 4), or marked sensory loss was combined with active reflexes (No. 5).

Examination of the past notes of these three equivocal patients added some further information. Patient 3 had shown severe sensory loss on his original admission two and a half years before, with impairment and delayed response to pin-prick over the cuirasse area (D3-D8), over the ulnar border of the forearm and little finger, and also in the lower limbs. Light touch and temperature sense had also been impaired over these areas, although position sense had appeared normal. He had made a very marked clinical recovery following a course of penicillin, but was still markedly ataxic in his gait and was unable to stand with feet together and eyes closed without falling. At the time of the tremor recording, pain, touch, and temperature were normally appreciated in all areas. Vibration sense was normal in both hands but impaired at the ankles. Two-point discrimination was good in the upper limbs except over the little fingers, but was very poor in the feet, only a separation of 9-10 cm. being appreciated. Thus the whole picture was one of an originally severe sensory loss, now greatly improved, but with residual damage, most markedly manifest in the ataxic gait and Rombergism. The latter features might suggest that the muscle and joint afferents were still fairly severely affected.

Patient 4 had also been originally admitted two and a half years before the tremor was recorded, but his sensory loss at this time was much less severe than that of Patient 3 and was limited to a variable slight diminution to pin-prick and temperature over the chest and ulnar border of both arms and in both legs below the knee. There was no diminution to light touch except over both feet. Joint position sense and two-point discrimination were accurate in all the fingers of both hands, and both stance and gait had been specifically reported on at the time as being normal. There thus seemed little or no subsequent change in a picture which suggested definitely milder sensory damage than in the case of Patient 3, but in which, nonetheless, no tendon jerks could be elicited.

Patient 5, on the other hand, showed a marked but " patchy " type of sensory loss, with a variable and often delayed response to pin-prick on the face, trunk, and lower limbs, and in the upper limbs, particularly along the ulnar border. Patches of complete analgesia alternated with areas of hyperalgesia. Of the other modalities, light touch was defective on the trunk, lower limbs, and ulnar border of the upper limbs but was normally appreciated over the face. Position sense was grossly diminished in all joints of the lower limbs and in the fingers, where movement but not direction could be appreciated, but was normal at the wrists, elbows, and shoulders. His gait was still ataxic and wide-based, but had improved

TABLE I

DEGREE OF DEAFFERENTATION

	Deep Reflexes of Right Upper Limb				Sensory Loss to		
	Biceps Jerk	Triceps Jerk	Supinator Jerk	Finger Jerk	Pin-prick	Cotton Wool	Position Sense
Patient 1	—	—	—	—	Severe	Slight	Severe
Patient 2	—	—	—	—	Severe	Severe	Slight
Patient 3	—	—	—	—	No loss*	No loss*	No loss*
Patient 4	—	—	—	—	Slight	No loss	No loss
Patient 5	—†	++	—	—	Marked	Marked	Marked
Patient 6	+R	+	+R	++	No loss	No loss	No loss
Patient 7	++	+	+	±	Marked	No loss	No loss
Patient 8	+++	++	++	++	No loss	No loss	No loss

*Had been severe, but recovered following penicillin (see text).
†Present and active at last previous examination 14 months previously.
+R = present on reinforcement only.

since his original admission, following penicillin treatment. The muscular reflex responses were also affected in a somewhat "patchy" and variable way. Of the tendon jerks in the right upper limb only the triceps was present at the time of the tremor recording. However, in the left arm the biceps, triceps, and supinator could all be elicited and even the finger jerk was obtained on reinforcement. None of the jerks could be evoked in either of the lower limbs. Examination of the past notes revealed that the right biceps jerk had not only been present, but active, at the last previous examination fourteen months before, at which time the right triceps jerk (now quite active) had been unelicitable. Tendon jerks had been consistently absent in the lower limbs since his first admission six years before. In his case, deafferentation appeared to have affected cutaneous sensation and tendon reflexes severely, but in an incomplete and variable distribution.

Characteristics of Tremor Spectrum.—Tremor in healthy subjects shows a base line of activity at all frequencies, but there is an increase between about 5 and 15 c./sec. with a distinct peak at 8 to 10 c./sec. (Halliday and Redfearn, 1956). It is increased in amplitude by loading the finger with weights, while the peak frequency is not greatly changed. Figs. 1, 2, and 3 show frequency spectra obtained from 46 healthy subjects (Halliday and Redfearn, 1956) compared with the present group of tabetic patients. Fig. 1 presents spectra for the unloaded finger, Fig. 2 for the finger with a 50 g. weight strapped beneath the terminal phalanx with cellulose tape, and Fig. 3 shows the same with a 100 g. weight attached. In contrast to the frequency, tremor amplitude varies greatly between different healthy individuals. The frequency spectrum from the healthy individual with the greatest amplitude in each case has therefore been plotted along with the average spectrum for the healthy group.

For clarity of presentation, the tabetic patients have been divided into two groups, namely, patients 1 to 3 and patients 4 to 8. It was found impracticable to include data from all eight patients on one graph, and in any case the spectra seem to fall naturally into these two groups.

It is clear from the figures that on the whole the tabetic patients show a higher general level of activity than normal. This increase is quite apart from any effect on the 5 to 15 c./sec. waveband, and is seen as a generalized raising of the base line throughout the spectrum; it seems particularly marked at the lower frequencies. This higher general level of random activity seems to affect the tabetic group as a whole and is not confined to the most severely deafferented.

However, it is with the 8 to 10 c./sec. rhythm of tremor, rather than with the random element, that this paper is mainly concerned. Whatever the finger loading, this peak is seen to be completely absent in patients 1 to 3. Patients 4 and 5 show little or no peak in the case of the unloaded finger, but a normal or high peak when the finger is loaded. Patients 6 to 8 always show a well-marked or abnormally high peak in all cases and especially when the finger is loaded.

Compared with the mean spectrum of the healthy subjects, in which the peak mean frequency shows little change on loading (Figs. 1 to 3), the peak tremor frequency of those tabetics with the less severe deafferentation is markedly slowed when the weight on the finger is increased, especially from 50 g. to 100 g. Data for peak frequency and load are given for each patient in Table II and show a change of as much as 4 c./sec. in all save one of the tabetics, to be compared with a change of 1 c./sec. in the healthy group.

Figs. 1 to 3 (*a*) show an apparent slowing of 3 c./sec. in the peak frequency of the "highest normal" spectrum after loading. This effect is purely accidental and results from the fact that the "highest normal" curves come from a different individual for each load. Thus the normal subject showing the most tremor of the unloaded finger was not the same subject as the one who showed most tremor with a 50 g. weight attached, and again was different for the 100 g. weight. The three individuals had different peak values, as can be seen in Table II, but none of the individuals showed more than a 1 c./sec. change of peak frequency with loading.

TABLE II

CHANGE OF PEAK FREQUENCY WITH LOADING

	Peak Frequency (c./sec.)			Maximum Change of Peak Frequency
	Unloaded	50 g.	100 g.	
Healthy subjects (mean)	9	10	9	1
Healthy subject with highest tremor level for unloaded finger (Fig. 1)	10	10	10	0
Healthy subject with highest tremor level with 50 g. attached (Fig. 2)	8	8	8	0
Healthy subject with highest tremor level with 100 g. attached (Fig. 3)	8	8	7	1
Patient 4	10	8	6	4
Patient 5	11	10	7	4
Patient 6	10	7	6	4
Patient 7	8	8	7	1
Patient 8	9	10	6	4

Discussion

In considering the implications of these results it should be realized that in none of the hundred or more healthy subjects so far examined have we failed to demonstrate the characteristic peak in the tremor spectrum in the neighbourhood of 9 c./sec.,

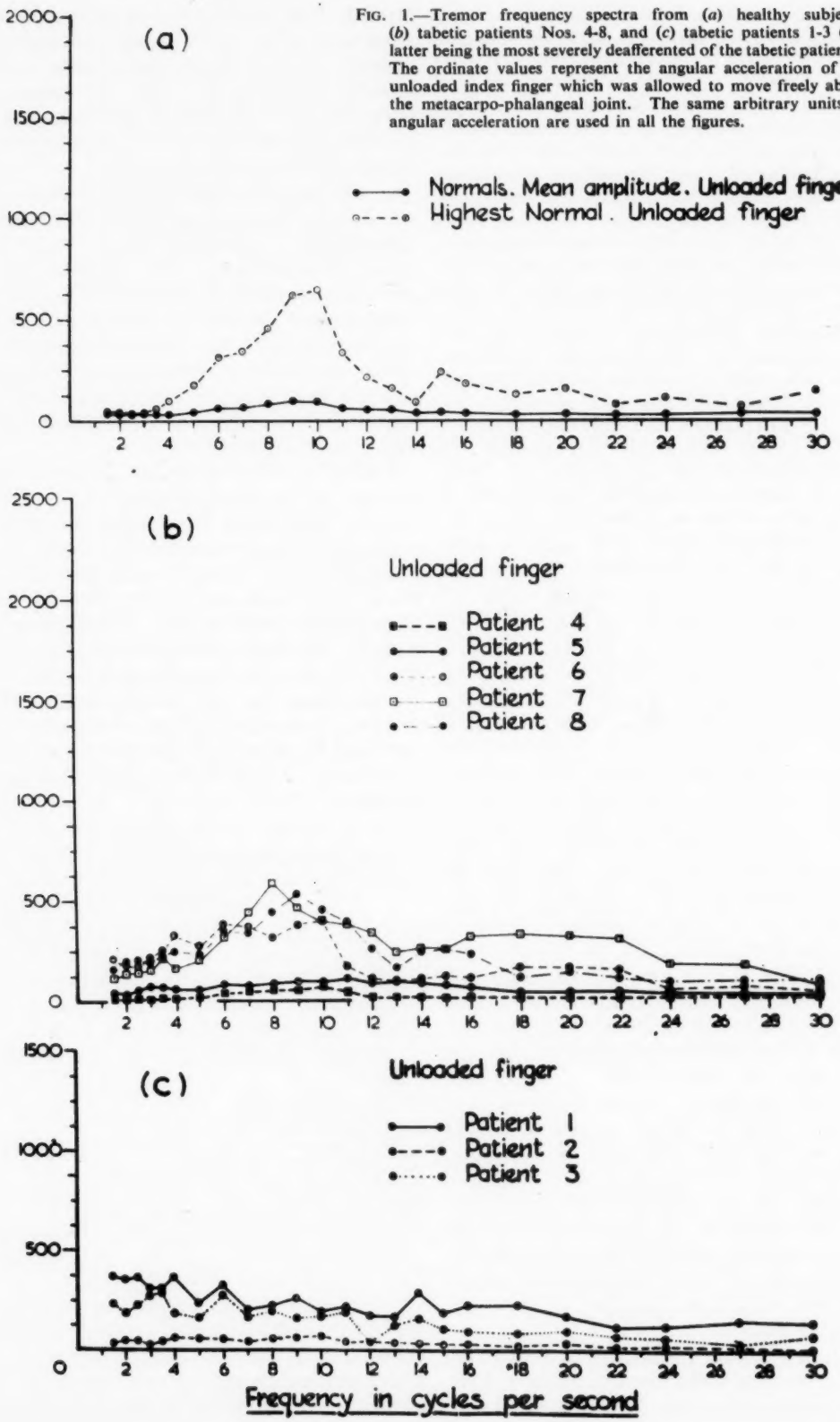
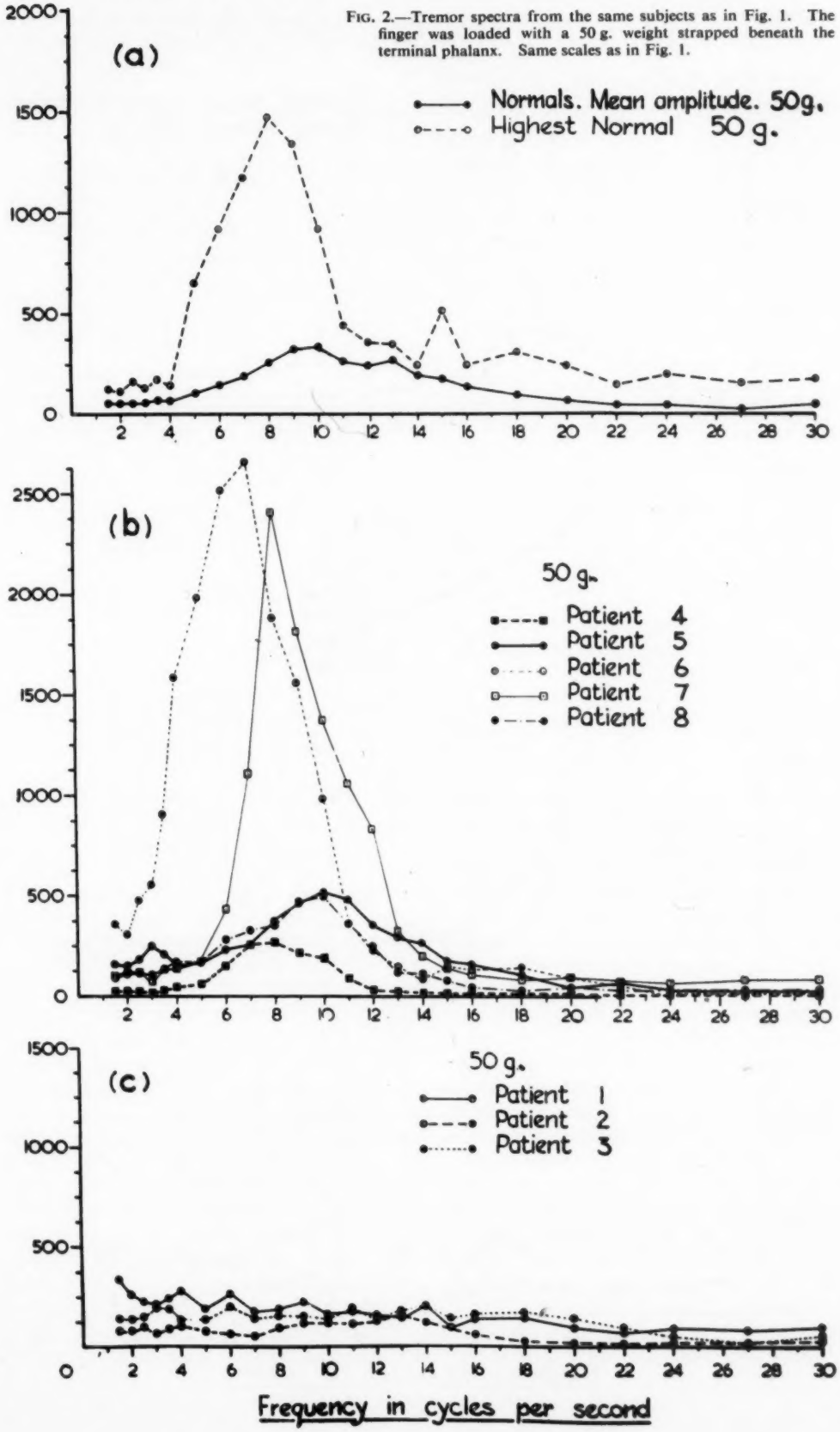


FIG. 1.—Tremor frequency spectra from (*a*) healthy subjects, (*b*) tabetic patients Nos. 4-8, and (*c*) tabetic patients 1-3 (the latter being the most severely deafferented of the tabetic patients). The ordinate values represent the angular acceleration of the unloaded index finger which was allowed to move freely about the metacarpo-phalangeal joint. The same arbitrary units of angular acceleration are used in all the figures.

FIG. 2.—Tremor spectra from the same subjects as in Fig. 1. The finger was loaded with a 50 g. weight strapped beneath the terminal phalanx. Same scales as in Fig. 1.



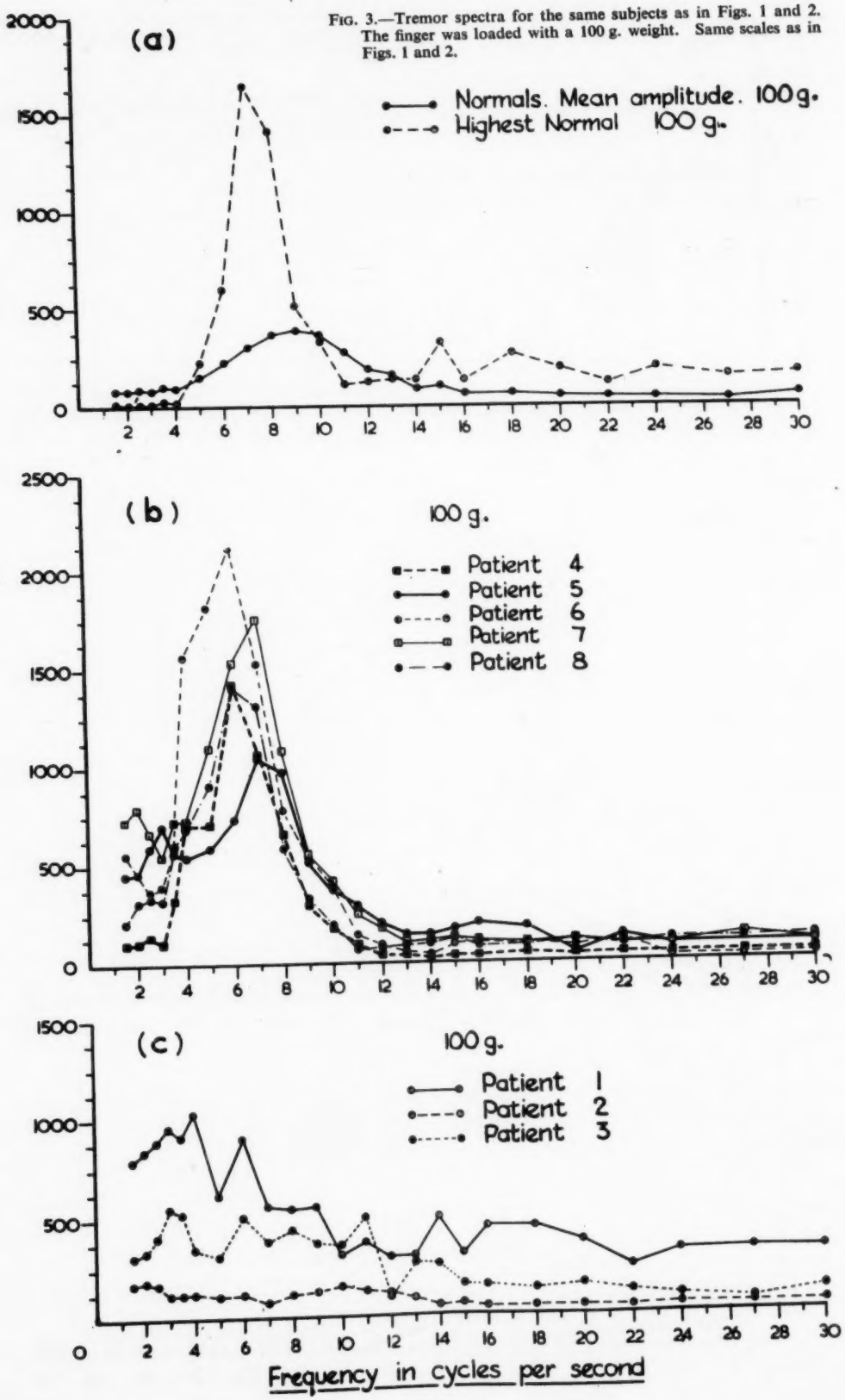


FIG. 3.—Tremor spectra for the same subjects as in Figs. 1 and 2. The finger was loaded with a 100 g. weight. Same scales as in Figs. 1 and 2.

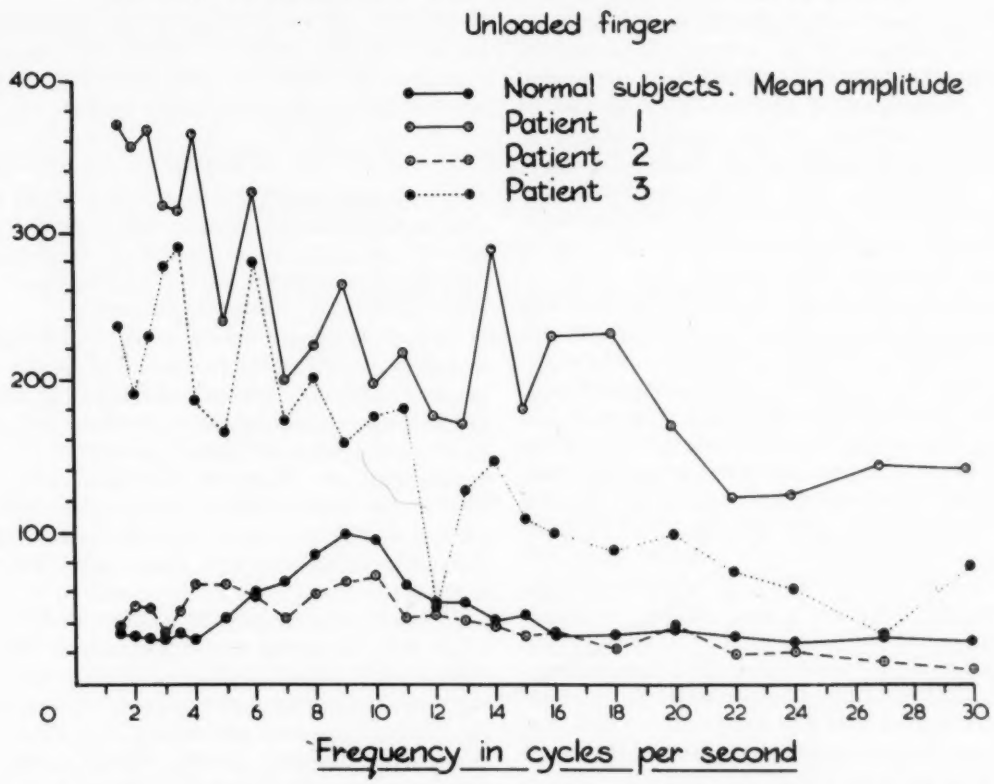


FIG. 4.—Tremor spectra for normal and severely deafferented tabetic subjects compared. The mean spectrum for a group of normal subjects is the same as in Fig. 1 (*a*), and the tabetic spectra are the same as in Fig. 1 (*c*). The same units are used as in Fig. 1, but the ordinate scale has been lengthened so that the contrasting shapes of the normal and of the deafferented spectrum may be seen more clearly.

although in some subjects it only becomes obvious on loading the finger in the manner described. The first three tabetic patients of the present series are quite distinct in this respect, as appears even more clearly if the ordinate scales of Fig. 1 are lengthened (Fig. 4). Though the mean level in the healthy subjects is lower than that shown by the tabetics, the latter do not show any signs of the clear and consistent rise to a maximum amplitude at 9 c./sec. characteristic of the normal subjects. The absence of this peak, of course, becomes even more evident when the amplitude of tremor in the healthy group is increased by loading (Figs. 2 and 3).

Of the three patients having no 9 c./sec. peak, two are certainly the most severely deafferented of the whole series; the third was either the third or the fourth most severely deafferented, and clinical evidence has already been adduced for rating him third. All three patients were without detectable tendon jerks in the right upper limb. There was a fourth patient without demonstrable tendon jerks who nevertheless showed the peak. In this series, therefore, an absent 8 to 10 c./sec. rhythm was always accompanied by absent tendon jerks, although the absence of jerks was not in every case associated with the absence of the rhythm.

In considering the anomalous patient (No. 4), the fact that the sensory deficit was limited to slight loss to pin-prick, while light touch and position sense were unimpaired, suggests that the damage to afferents cannot have been so severe as the absence of jerks might have suggested. Some allowance may also be due for the inaccuracies and approximations implicit in clinical testing. Moreover, if the hypothesis is maintained that the tremor rhythm is due to oscillation in the stretch reflex of the muscles concerned, the tendon jerks of other muscles, even though of neighbouring ones, cannot be taken as a reliable measure of the state of the reflexes in the actual muscles concerned. Hence, perhaps, the higher correlation when other sensory phenomena are taken into account. In any case it is not yet clear whether the tendon jerk is a measure of that aspect of the stretch reflex which is relevant to tremor. It is well known that the tendon jerk and the stretch reflex do not always behave in the same way. Indeed, in the cat the tendon jerk may be highly active when the stretch reflex has been depressed, and it may

come and go quite independently of the level of spindle firing (Granit, 1955). Granit, Henatsch and Steg (1956) have produced evidence that the phasic and tonic components of the muscle's response to stretch may be mediated by two distinct groups of motor neurones. It is not yet clear what role these different mechanisms play in the production of tremor, but the existence of such a differentiation emphasizes how inadequate the tendon jerk may be as an index of stretch reflex activity.

The disappearance of the 9 c./sec. rhythm in the deafferented cases is consistent with the hypothesis that the tremor is due to an oscillation in the reflex arc. However, this is not the only possible explanation of this observation. Rhythmical activity fed down from the central nervous system through the gamma efferent fibres to the muscle spindle (and only reaching the alpha motor neurones indirectly via the afferent fibres) might disappear in much the same way after deafferentation. But the behaviour of the tremor rhythm in those cases with only partial deafferentation provides some further evidence which seems to be in favour of the " servo " hypothesis. The increased sensitivity of the frequency to loading in these cases compared with the normal is strongly suggestive of the behaviour of a failing " servo " mechanism with insufficient energy at its disposal to cope with the increased load. If the rhythm were of central origin but transmitted via the gamma efferents, increasing the load in a partially deafferented case would be expected to diminish the amplitude and leave frequency unaltered, whereas in fact amplitude is increased and frequency diminished.

The high levels of tremor amplitude at 7 to 9 c./sec. reached by the partially deafferented tabetic cases poses an interesting problem. One possibility might be that, with the destruction of some of the stretch reflex arcs, the remainder were being run at a high loop gain by increased gamma activity as a compensation. This hypothesis may receive some support from the fact that tendon jerks are erratically brisk in some of these cases. Further, the fact that the peak amplitude is not increased, but diminished, in the two most tremulous patients when the load is increased from 50 to 100 g. suggests that the available loops may even have reached saturation in these cases and may be oscillating to the full extent of their power. Such a failure to increase tremor amplitude by loading at these relatively low tensions has not been seen in any other cases.

Summary

It has been suggested in a recent paper that the characteristic tremor rhythm with a peak frequency of 8 to 10 c./sec. is unaffected by deafferentation, and this has been put forward as evidence against the " servo loop " theory of tremor.

In this paper the results of recording and automatically analysing the frequency of tremor in eight tabetic patients showing varying degrees of deafferentation is presented. In the most severely deafferented patients there is no sign of the normal tremor rhythm. In the other patients, who showed less severe sensory loss, the tremor rhythm was present and of greater amplitude than normal, and the peak frequency was abnormally lowered by loading.

These results suggest that the integrity of the reflex arc is essential to the presence of the tremor rhythm and they provide some support for the " servo " hypothesis. Moreoever, the behaviour of the tremor frequency on loading in the less severely deafferented patients showed characteristics which would be expected if it was produced by oscillation in a failing " servo " but not if it was a centrally determined rhythm.

We should like to thank the physicians of the National Hospital, Queen Square, who put their cases at our disposal, Dr. W. A. Cobb for lending us the automatic frequency analyser, and Dr. E. A. Carmichael for his interest and encouragement.

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SENSORY NERVE ACTION POTENTIALS IN PATIENTS WITH PERIPHERAL NERVE LESIONS

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In 1949 Dawson and Scott described a method of examining sensory impulses in human peripheral nerves. By their technique, the median or ulnar nerve at the level of the wrist was stimulated electrically using single shocks, and the action potential of the afferent volley recorded through surface electrodes placed over the nerve trunk at a higher level in the arm. The afferent volley contained both sensory impulses and antidromic impulses in motor fibres and gave rise to a small diphasic or triphasic potential with an amplitude of less than 50 microvolts and a duration of 2 to 3 milliseconds. To eliminate the contribution of motor fibres, Dawson (1956) modified his original technique and stimulated the digital nerves through small ring electrodes wrapped round the fingers, the afferent volley being recorded as before through surface electrodes placed over the median or ulnar nerve trunk in the arm. The sensory potentials recorded were similar in form to the mixed nerve action potentials obtained previously, but, being derived from digital nerves, they were considerably smaller in amplitude.

In view of Dawson's findings it seemed worthwhile to investigate the behaviour of sensory action potentials in patients with peripheral nerve lesions, and the present paper is based on some 50 cases examined in this way. In general the technique has proved to be of considerable value in the clinical assessment of patients, and in certain cases it has provided more information about sensory nerve function than could be obtained by formal sensory testing.

Methods

These differed only in detail from those described previously by Dawson and Scott (1949) and by Dawson (1956). For stimulating the digital nerves, silver strips 2 to 4 mm. wide were used, covered by lint moistened in saline and firmly wrapped round the finger, with the cathode placed near the metacarpo-phalangeal joint and the anode in the region of the terminal interphalangeal joint. The stimulus itself was a brief condenser discharge (time constant approximately 70 microseconds) delivered through an isolating transformer. Surface recording electrodes were of the "saddle" pattern described by Dawson and Scott (see their Fig. 1) with an inter-electrode distance of 3 cm. Before applying the recording electrodes, the course of the median or ulnar nerve in the arm was usually mapped out by stimulation and observation of the motor response. In the few patients without any motor response to nerve stimulation the course of the nerve could not be determined in this way; in such a case recording electrodes were placed over the expected position of the nerve trunk and adjusted to give the largest response to sensory stimulation. The design of the recording electrodes was such that small lateral movements had little or no effect on the size of the recorded potential; they were thus particularly suitable for rapid tests on patients.

Nerve action potentials were amplified in the conventional way and displayed on a cathode ray tube. For photography, the method of superimposition used by Dawson (1947) was adopted; with the sweep of the cathode ray tube locked to the stimulator, records were obtained by photographing 20 successive sweeps at one-second intervals, all 20 being superimposed on the same piece of film. This has the effect of emphasizing potentials occurring at a fixed time in the sweep, random potentials merely producing a thick base line from which even small nerve potentials can be distinguished.

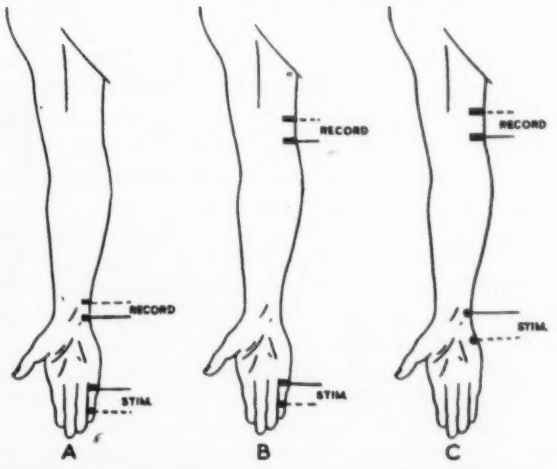

FIG. 1.—Positions used for stimulating and recording electrodes.

When stimulating the fingers the two sites for recording electrodes used by Dawson were at the level of the wrist (Fig. 1A) and just above the elbow (Fig. 1B). In our own experience sensory action potentials recorded from the elbow region were always small and in some obese but otherwise normal subjects they were absent altogether. For this reason recording at wrist level or just above it was preferred as a standard arrangement, the stimulus being applied to the index finger when testing the median nerve and to the fifth finger for the ulnar nerve. In a few patients stimulation of the median or ulnar nerve trunk at the wrist was used with recording electrodes just above the elbow (Fig. 1C); with this arrangement the nerve action potential is large and easy to record, and although it is made up of antidromic motor as well as sensory impulses it may provide useful supplementary information.

All tests were carried out in a warm room with the subject lying on a couch and covered with blankets. Before examining people with cold hands, the arms were immersed in hot water for five or 10 minutes before the session, but no other method of controlling temperature was attempted.

No children were examined, and since nerve conduction velocity is known to decrease in the elderly (Wagman and Lesse, 1952), patients over the age of 70 were excluded from the present series.

Full relaxation of the subject during a test was essential as records were easily spoilt by persistent muscular contraction, motor unit action potentials being 10 or 100 times as large as the nerve potential. With patience, relaxation could usually be obtained but on a few occasions when examining apprehensive or uncooperative subjects it was necessary to give an intravenous barbiturate to cover the procedure.

Results

Control Observations on Healthy Nerves.—Sensory nerve action potentials recorded from the wrist in a healthy subject are shown in Fig. 2. In this case the triphasic form of the action potential is clearly shown, the most prominent feature being the second (upward) deflection during which the lower recording electrode becomes negative with respect to the upper one. When recording small potentials this

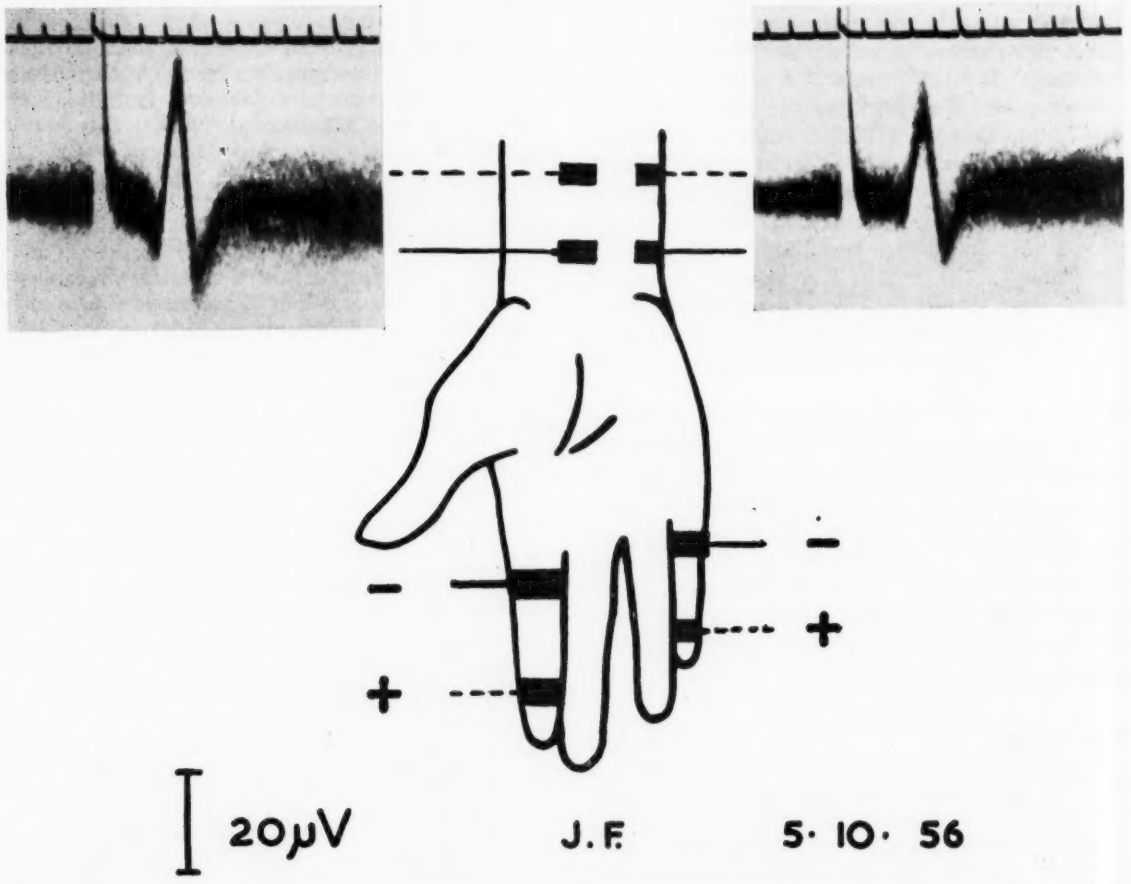

FIG. 2.—Normal sensory action potentials recorded from the median and ulnar nerve trunks at the wrist in a healthy subject. Stimuli to index and little fingers. Tracings show stimulus artefact followed by triphasic action potential. Time scale 1 and 5 milliseconds; 20 sweeps superimposed.

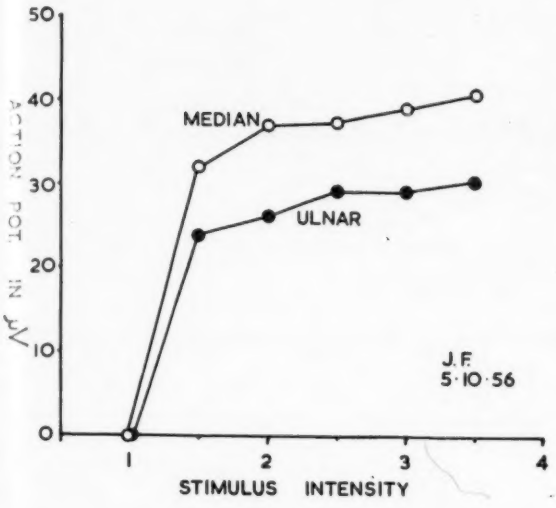

FIG. 3.—From the same experiment as in Fig. 2 to show relation between stimulus intensity and the size of sensory potentials recorded. Stimulating voltages expressed as multiples of threshold value.

triphasic form may be lost, the upward deflection still appearing but the other phases being scarcely discernible in superimposed records.

The relation between stimulus intensity and the size of the nerve response is shown in Fig. 3, from which it can be seen that the nerve action potential appears rather abruptly with increasing stimulus strength, and that above a certain critical stimulus intensity there is little further increase in action potential amplitude. With most of our normal subjects it was possible to use a stimulus intensity above this critical value, so that a further increase produced little change in the recorded potential. Strong shocks applied to the fingers produce considerable local pain, so that maximal stimuli cannot be attempted, but from what has been said above, it may be assumed that most of the large myelinated fibres in the digital nerves were being stimulated in each case. A few subjects were unable to tolerate the repetitive stimuli required to obtain superimposed records and in such cases single sweeps were photographed.

With stimuli approaching as closely as possible the maximum that could be tolerated by each subject, the size of the recorded nerve action potentials varied considerably in different individuals. For this reason a large number of healthy nerves were examined to provide a range of normal values. These control observations were made not only on healthy subjects working in the laboratory but also on the unaffected nerves of patients presenting isolated peripheral nerve lesions. In all, 28 median and 39 ulnar nerves were examined as controls.

Results of the control measurements are shown in Fig. 4, from which it can be seen that the potentials recorded from the median nerve at the wrist varied in peak-to-peak amplitude from 9 to 45 microvolts, whereas those recorded from the ulnar nerve at the wrist were generally rather smaller with a range of 8 to 28 microvolts.

For each subject the latency of the nerve action potential was measured; owing to the variability of the initial phase of the action potential, latencies were measured from the stimulus artefact to the peak of the main (negative) deflection, and in Fig. 5 this figure has been plotted for each case against the conduction distance from stimulating cathode to the lower recording electrode. For the median nerve, action potential latency varied from 2·5 to 4 milliseconds. Action potential latencies for the ulnar nerve were generally slightly shorter than for the median (range 2·2 to 3·4 milliseconds), but when the figures are corrected for conduction distance the apparent difference between the two nerves disappears.

Median Nerve Lesions at the Wrist.—Twenty-nine patients were examined with suspected median nerve compression in the carpal tunnel. These were patients referred by members of the hospital staff for routine electrodiagnosis between January, 1956, and May, 1957, and as there was no selection of cases on our part, the group as a whole contained a proportion of doubtful and atypical cases. Wasting of the thenar muscles was recorded in the hospital notes of five patients and muscular weakness without wasting in a further three. Sensory impairment, which usually took the form of mild subjective loss of superficial sensation in the fingers, had been noted in 14 cases.

When the index finger was stimulated electrically, it was noticeable that some of the patients would tolerate a higher stimulating voltage than the control group. Since we were attempting to produce a sensory action potential whenever possible, stimulus intensity was kept as high as could be tolerated by each individual but, in spite of this, the action potential recorded from the median nerve just above the wrist was frequently reduced in size. Action potential amplitude (peak-to-peak) in each case is shown in Fig. 4, from which it can be seen that the nerve action potential was absent altogether in six cases and of small amplitude in many others. Latency to the peak of the main deflection of the action potential was measurable in 23 cases, and Fig. 5 shows that it was often increased, although conduction distances were generally similar to those in the control group.

A detailed correlation between electrical and

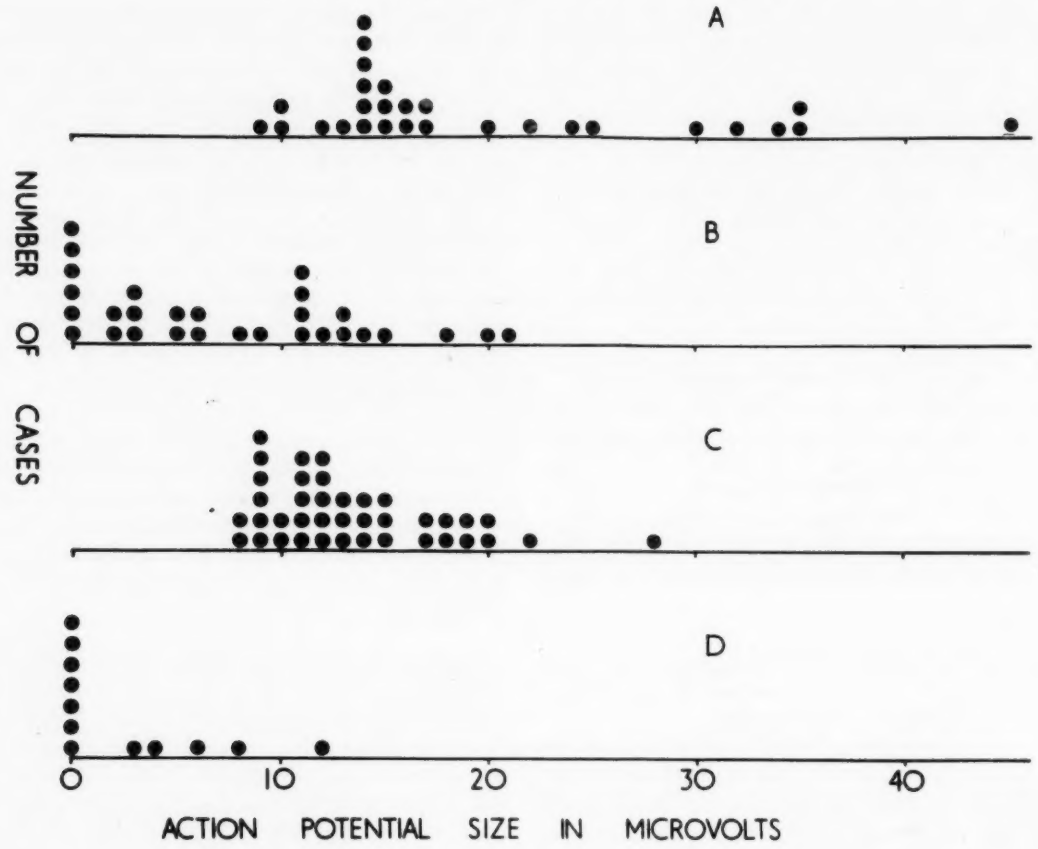

FIG. 4.—Sensory action potential amplitude in different individuals. All potentials recorded at the wrist.

(*A*) From the median nerve during stimulation of the index finger in control subjects.
(*B*) The same in patients with suspected median nerve lesions.
(*C*) From the ulnar nerve during stimulation of the little finger in control subjects.
(*D*) The same in patients with suspected ulnar nerve lesions.

clinical findings is prevented by the difficulty of expressing minor degrees of sensory loss in an objective or quantitative manner, but in general there is no doubt that the nerve action potential was most likely to be abnormal in patients who showed obvious sensory defects. For example, there were 15 patients with suspected median nerve lesions in whom sensation was normal on clinical testing; the sensory action potential was absent in one of them and less than 5 microvolts in amplitude in another. In eight patients with some impairment of superficial sensation on the fingers but without any defect of two-point discrimination there were two with absent nerve action potentials, and two others with potentials which were less than 5 microvolts in amplitude. There were six patients with defective two-point discrimination on the fingers in addition to superficial sensory impairment to pin-prick and cotton wool, and nerve action potentials were absent in three of them; in the remaining three patients recorded potentials were all less than 5 microvolts in amplitude.

In the patients without sensory loss, action potential latencies of less than 4 milliseconds were recorded in seven cases. In patients with some clinical sensory disturbance but without defects of two-point discrimination, latencies of less than 4 milliseconds were found in two cases. In the group of patients with two-point loss, a latency of less than 4 milliseconds was found in only one case.

Recovery of Nerve Action Potential after Operation on Carpal Tunnel.—Repeated observations on patients after operation were possible in 10 cases, and in all of them some recovery of the nerve action potential was seen. These serial observations were not continued for as long as we would have liked, as few patients were prepared to attend for tests on more than one or two occasions after their symptoms had disappeared, and in general the patients' symptoms seemed to resolve a considerable

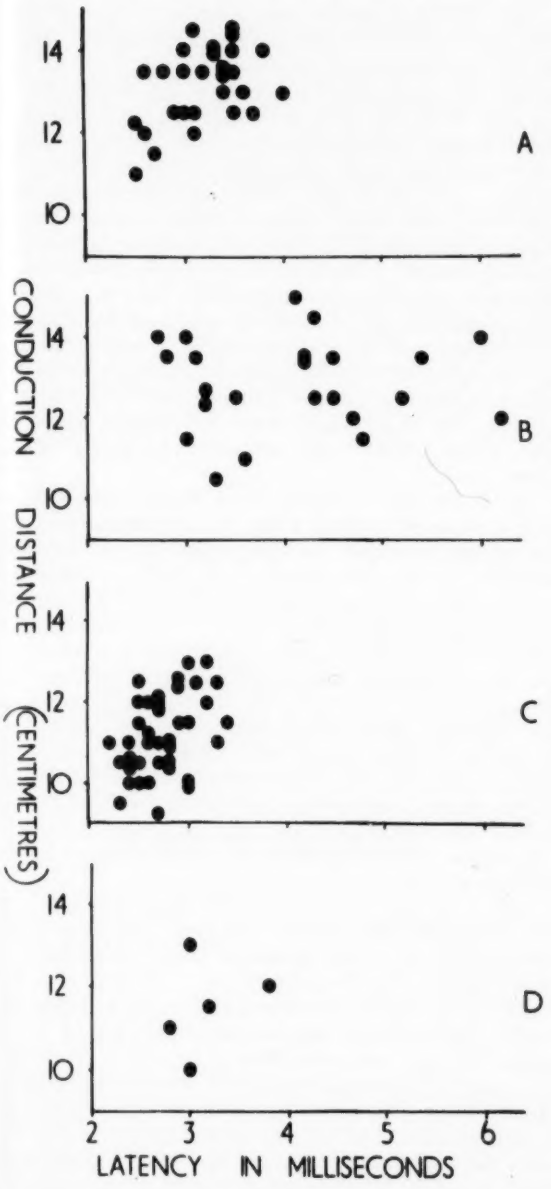

FIG. 5.—Sensory action potential latency in different individuals plotted against conduction distance (stimulating cathode to wrist electrode) in each case. Groups *A*, *B*, *C*, and *D* as in Fig. 4.

time before the nerve action potential became normal. These points are illustrated by the following case history.

Mrs. C. B., a 48-year-old housewife, was admitted to the National Hospital in May, 1956, with the complaint of pain and numbness in the right arm during the preceding year. She was awakened at night by numbness of the right hand and forearm accompanied by aching pain deep in the palm and in the muscles of the forearm, these symptoms lasting for up to an hour. After a few months she developed tingling sensations in the right thumb, index and middle fingers; at first these occurred only at night but later they persisted throughout the day, being made worse by using the hand. Examination on admission revealed weakness of the abductor pollicis brevis and subjective sensory impairment to pin-prick and cotton wool over the thumb, index and middle fingers, and over the median-supplied half of the ring finger. Appreciation of joint movement was intact in the digits, but on the pad of the index finger the patient made errors in discrimination of compass points 0·5 cm. apart; there were no errors at 0·75 cm. separation on the index finger or at 0·5 cm. on the little finger.

Sensory action potentials were examined with ring stimulating electrodes round the index finger and surface recording electrodes over the median nerve trunk just above the wrist (conduction distance, 13·5 cm.). A small action potential, approximately 3 microvolts in amplitude, was recorded which could not be made larger by increasing the intensity of the stimulus. Action potential latency measured from the stimulus artefact to the peak of the main upward deflection was 5·4 milliseconds (Fig. 6A).

The right flexor retinaculum was divided by Mr. J. Hankinson, and clinical improvement was rapid. When seen on the 27th post-operative day, the patient was symptom free and no sensory deficit could be detected in the right hand. The electrical test was repeated with the same electrode positions and stimulating voltage as before, and it showed a sensory action potential with an amplitude of 11 microvolts and a latency of 4·1 milliseconds (Fig. 6B). Although sensation appeared clinically to have returned to normal within a month of operation,

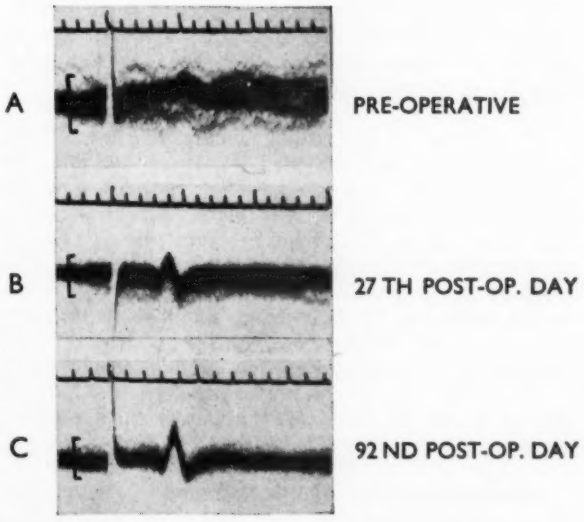

FIG. 6.—Mrs. C. B.: carpal tunnel syndrome.

Recordings from the median nerve at the wrist during stimulation of the index finger before and after division of the flexor retinaculum. Tracings show stimulus artefact followed by nerve action potential in each case.

Calibration 20μV. Time scale 1 and 5 milliseconds; 20 sweeps superimposed.

a third electrical test was carried out on the 92nd post-operative day (Fig. 6c) which showed further improvement in both action potential size (19 microvolts) and latency (3·7 milliseconds).

At the time of each test, control observations were made on the ulnar nerve at the wrist during stimulation of the little finger. Sensory action potentials recorded from the ulnar nerve were not significantly different in the pre- and post-operative periods, the figures for action potential amplitude being successively 10·8, 11·0, and 10·5 microvolts. On all three occasions ulnar action potential latency was between 2·6 and 2·8 milliseconds.

Ulnar Nerve Lesions at the Elbow.—Twelve patients with suspected ulnar nerve lesions at the elbow were examined. Wasting of the ulnar-supplied muscles was present in nine patients and weakness without wasting in two others. Subjective impairment of superficial sensation in the ulnar territory was present in 11 patients and discrimination of compass points on the little finger was defective in six of them.

Sensory nerve action potentials were examined with stimulating electrodes round the little finger and recording electrodes over the ulnar nerve trunk just above the wrist. Stimulus intensity was kept as high as could be tolerated by each individual but, in spite of this, nerve action potentials were absent in seven cases and of small amplitude in several others (Fig. 4).

Action potential latency could only be measured in five patients and in none of them was it obviously abnormal (Fig. 5). In one patient, however, a small increase in latency was thought to be present as shown by comparison between the affected hand and the ulnar nerve on the opposite side.

The patient, a 50-year-old housewife, showed mild weakness of the ulnar-supplied muscles on one side with subjective impairment of superficial sensation over the little finger and half of the ring finger, but with preservation of two-point discrimination. When the little finger on the affected side was stimulated, an action potential 8 microvolts in amplitude was recorded from the wrist, its latency being 3·8 milliseconds (conduction distance, 12 cm.). When the little finger on the opposite side was stimulated in the same way, the ulnar action potential at the wrist was 11 microvolts in amplitude with a latency of only 2·7 milliseconds although the conduction distance was the same (12 cm.).

When patients with suspected ulnar nerve lesions showed a sensory action potential at the wrist which was only doubtfully reduced in size, more information was sometimes obtained by stimulating the nerve trunk at the wrist, and recording the mixed sensory and antidromic motor volley from the ulnar nerve above the elbow. The findings in one such case are described in detail below.

Mr. G. S., aged 56, was referred to one of us in October, 1956, with a history of numbness and tingling in the fourth and fifth fingers of the left hand for four weeks. In the past, it had not been uncommon for him to wake in the mornings with transient numbness of the ulnar fingers, but in September, 1956, he had awakened with numbness which did not disappear as it had done before. Examination four weeks after the onset showed slight weakness of the ulnar-supplied muscles in the left hand without wasting. Power in the flexor carpi ulnaris seemed normal. There was a subjective change in the sensation aroused by a firm touch on the one and a half fingers supplied by the ulnar nerve and on the ulnar side of the hand, without real impairment of appreciation of pin-prick or cotton wool. There were, however, occasional errors in discrimination of compass points 0·5 cm. apart on the fifth finger which were not present elsewhere. The ulnar nerve itself was not thickened at the elbow.

When the left abductor digiti minimi was sampled with a concentric needle electrode, the electromyograph showed no abnormal insertion activity or spontaneous fibrillation, and the number of motor units under voluntary control was not obviously reduced. Conduction velocity in the motor fibres of the left median and ulnar nerves was measured with stimulating electrodes placed just above the wrist and elbow, and recording electrodes (concentric needles) in the abductor pollicis brevis and the abductor digiti minimi respectively. There was no difference in conduction rate between the two nerves distal to the wrist, but in the segment which included the elbow region, calculated conduction velocity for the fastest motor fibres in the ulnar nerve was 35 metres per second as opposed to 52 metres per second for the median nerve.

Sensory action potentials were examined with ring stimulating electrodes round the index and little fingers and surface recording electrodes over the median and ulnar nerve trunks just above the wrist (Fig. 7). The ulnar action potential was rather small (amplitude 6 microvolts) compared with the median (amplitude 18 microvolts), but was not considered to be clearly abnormal. The median and ulnar nerve trunks were then stimulated at wrist level, with recording electrodes above the elbow. A normal afferent volley was recorded without difficulty from the median nerve in this way, but from the ulnar nerve a small delayed action potential was obtained which could not be made larger by increasing stimulus intensity.

Brachial Plexus Lesions.—Two patients were examined with severe sensory loss in the hand due to a lesion of the brachial plexus. In both cases the brachial plexus on one side was invaded by malignant deposits, the site and nature of the lesion being confirmed by exploration and biopsy. In neither case could a sensory nerve action potential be detected at the wrist when the affected fingers were stimulated whereas normal potentials were obtained without difficulty in the opposite arm. In one patient with invasion of the lower trunk of the brachial

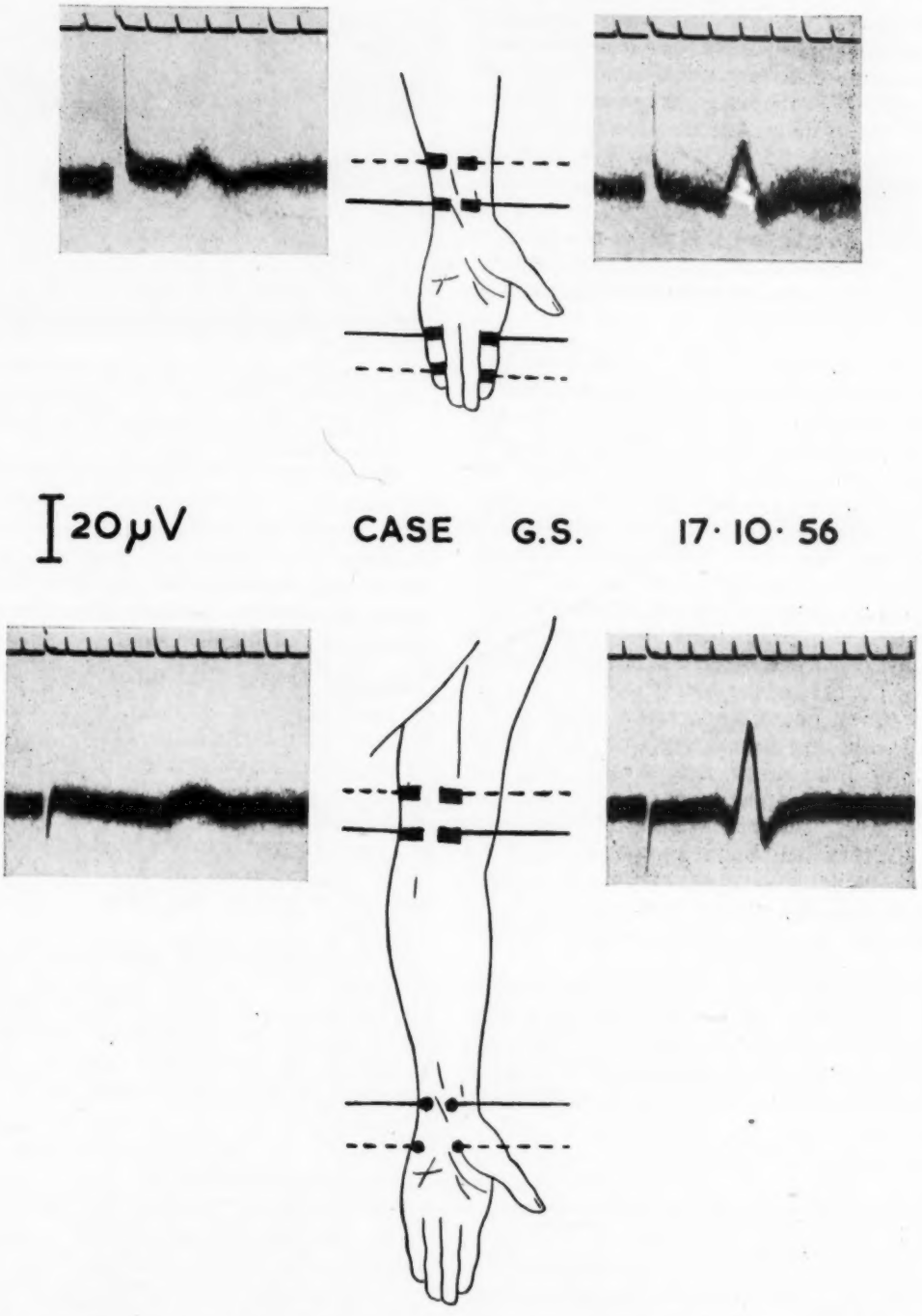

FIG. 7.—Mr. G. S.: ulnar nerve lesion at the elbow. Lower tracings show records from median and ulnar nerves just above the elbow during supramaximal stimulation of nerve trunks at the wrist. Upper tracings show sensory action potentials recorded at the wrist during stimulation of fingers. Time scale 1 and 5 milliseconds; 20 sweeps superimposed.

plexus by mammary carcinoma, sensory loss was confined to the inner side of the arm and hand and to the ring and little fingers, with sparing of the thumb and index finger and only doubtful subjective diminution in superficial sensation over the middle finger. In the little finger itself sensory loss

was severe, with almost complete superficial anaesthesia and considerable proprioceptive loss. In this patient no sensory nerve action potential could be detected in the ulnar nerve when the little finger was stimulated whereas a normal action potential (amplitude 15 microvolts) was recorded from the median nerve when the index finger was stimulated.

These findings serve to confirm the reliability of the technique in demonstrating changes in the distal part of a sensory nerve when the causal lesion is as high as the brachial plexus.

Polyneuritis.—Sensory nerve conduction was examined in seven patients with chronic polyneuritis of varying aetiology. All these patients showed symmetrical peripheral weakness with loss of tendon jerks and in all but one of them sensory loss was present in both hands and feet. In Table I a simple method of grading the motor and sensory signs in the hands has been used, which shows that the severity of involvement varied widely in different patients. All the patients were seen more than two months after the onset of their illness and one of them (Case E. W.) had made a substantial clinical recovery by the time of the test.

Sensory action potentials were examined in the usual way with ring stimulating electrodes round the index or little finger and surface recording electrodes over the appropriate nerve trunk just above the wrist. Sensory action potentials were absent in five patients although sensation appeared clinically to be perfectly preserved in one of them and to be only slightly affected in two others. In the remaining two patients small delayed sensory potentials were recorded (Fig. 8).

Motor nerve conduction velocity in the forearm was also examined in each case, stimulating electrodes being placed over the ulnar or median nerve trunk just above the wrist and elbow, with recording needle electrodes in the small muscles of the hand.

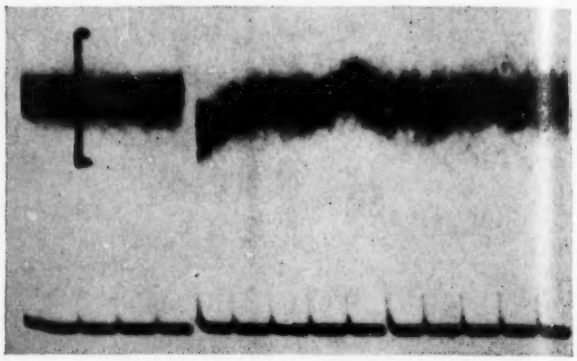

FIG. 8.—Mr. H. S.: progressive polyneuritis with retinitis pigmentosa and deafness. Clinical diagnosis Refsum's disease. Record from median nerve at the wrist during stimulation of index finger shows stimulus artefact followed by small delayed nerve action potential (conduction distance 12·5 cm.). Calibration 20μV. Time scale 1 and 5 milliseconds; 20 sweeps superimposed.

Slowing of motor nerve conduction, which is known to occur in polyneuritis (Lambert, 1956), was present in all seven of our patients (Table I), the degree of slowing showing little relation to the clinical state of muscle power.

Peroneal Muscular Atrophy.—Two patients with peroneal muscular atrophy were examined, the findings being included in Table I. Both patients showed the classical picture of pes cavus accompanied by slowly progressive wasting and weakness of the lower limbs, starting in their peripheral parts and spreading later to the thighs and to the upper limbs. In the case of patient L. S., an affected relative was examined and found to have a similar condition.

From Table I it can be seen that no sensory action potentials were recorded in either patient, and that marked slowing of motor nerve conduction velocity in the forearm was also present. The motor findings in Case G. M. have already been described in detail elsewhere (Gilliatt and Thomas, 1957).

TABLE I

POLYNEURITIS AND PERONEAL MUSCULAR ATROPHY

Case	Aetiology	Paralysis of Intrinsic Muscles	Sensory Loss in Fingers	Motor Nerve Conduction Velocity in Forearm* (metres/sec.)	Sensory Action Potentials	Nerve Examined
J. R.	Unknown	+++	+	25·9	Small delayed	Median
A. F.	Unknown	+++	+++	7·1	Absent	Median
E. S.	Polyarteritis nodosa	Complete	+++	Nerve inexcitable	Absent	Median
W. F.	Unknown	+	+	17·0	Absent	Ulnar
R. H.	Familial, hypertrophic	++	++	6·8	Absent	Ulnar
H. S.	Refsum's disease**	++	++	38·5	Small delayed	Median
E. W.	Familial, hypertrophic	+	No sensory loss	14·4	Absent	Ulnar
G. M.	Peroneal muscular atrophy	+++	+	11·2	Absent	Ulnar
L. S.	Peroneal muscular atrophy	++	+	26·4	Absent	Median

+ = slight ++ = moderately severe +++ = severe

*Normal range 46 to 67 metres/sec. (Thomas, Sears, and Gilliatt, to be published.)

**Clinical details of this patient are contained in a paper to be published by Dr. N. S. Gordon.

Discussion

Our results have confirmed Dawson's original observation that a small action potential can be recorded from the median or the ulnar nerve trunk at the wrist when brief electrical shocks are applied to the digital nerves in the fingers. In our study nerve action potentials appeared so constantly in control subjects that their absence has been regarded as a reliable sign of disturbed function. However, the potentials recorded from healthy nerves varied considerably in amplitude in different individuals, so that little significance has been attached to small variations in action potential size in pathological material. In doubtful cases, measurement of action potential latency was often helpful, particularly when a damaged nerve could be compared with an unaffected nerve in the same or the opposite arm. Latency measurements were most valuable in the group of patients with median neuritis at the wrist, values in excess of the longest control figure being found in more than half of them. This result may be compared with the marked slowing of motor nerve conduction which has been shown to occur in this condition (Simpson, 1956).

In attempting to relate clinical and electrical findings there are a number of difficulties. In the first place the sensory fibres contributing to the nerve action potential are believed to be large myelinated fibres, since their conduction velocity between wrist and elbow is at least as great as the maximal conduction velocity of motor nerve fibres supplying the small muscles of the hand (Dawson, 1956). Therefore these potentials provide no information about the small myelinated and non-myelinated fibres which are thought to be concerned with pain and temperature sensation. Of the large myelinated fibres contributing to the nerve action potential, some may be presumed to convey impulses from the skin whereas others supply deep structures such as joint capsules and periosteum. It must therefore be concluded that the nerve action potential does not provide direct information about the functional state of any single sensory modality.

In relating electrical and clinical findings there is a further complication which derives from the nature of the stimulus. To produce synchronous volleys we have used an electrical shock which is sufficient in a normal nerve to excite a large number of fibres. A damaged fibre, however, may still be capable of responding to physiological stimuli through its end-organ when its electrical threshold is so high that it no longer responds to a brief shock applied to the nerve trunk. This would have the effect of reducing or abolishing the potential that we attempt to record without exerting a comparable effect on sensory function.

The nerve action potential that we have recorded is formed from the summed potentials of a large number of nerve fibres, and its appearance depends upon the passage of a synchronous volley under the recording electrodes. Slowing of nerve conduction has the effect of scattering the time of arrival of different impulses at the recording electrodes and thus of reducing the peak amplitude of the compound action potential. Slowing might therefore be expected to produce more disturbance of the nerve action potential than of sensory function, and there is some support for this in our records. In the patients with polyneuritis, motor nerve conduction velocity was also measured and was often slowed to less than half the normal figure. In these patients the sensory nerve action potential was almost always absent, and yet some of them showed little or no deficit on formal sensory testing. This sort of result is most easily explained by the assumption that nerve conduction was grossly slowed in all large myelinated fibres, but lost completely in very few of them.

The site of the nerve lesion is of obvious importance in considering the relation between clinical and electrical findings. In patients with median neuritis at the wrist, the segment of nerve examined has always included the damaged portion, a fact which has enabled a high proportion of mild cases to be recognized. With ulnar nerve lesions at the elbow recording of sensory potentials at the wrist can only be expected to show changes if a proportion of fibres undergo degeneration in their distal parts. In mild ulnar nerve lesions more striking abnormalities may be demonstrated by stimulating the ulnar nerve trunk at the wrist and recording the mixed sensory and motor nerve action potential above the elbow. In the case of brachial plexus lesions we have not succeeded in devising any method of recording above the level of the lesion and have been forced to restrict ourselves to the observation of changes in the distal parts of the sensory nerves.

From what has been said above, it is clearly impossible to equate electrical and clinical findings in patients except in the most general terms. The relationship between electrical and clinical abnormalities varies not only in different pathological conditions but also in different individuals with the same condition, and even in the same person at different times, *e.g.*, before and after operation on the carpal tunnel. In general, however, it may be said that patients with severe sensory loss in the hand have all shown abnormalities of the nerve action potential whereas the reverse has not been true, several patients with abnormal or absent nerve potentials having been without demonstrable sensory loss.

As a diagnostic procedure, the method has the great advantage that it provides information about the function of sensory nerve fibres which is objective and obtained directly from the nerve, without any cooperation from the patient except insofar as he is required to lie still and relax during the test. From patients who are unable to cooperate at all the information can still be obtained by examination under anaesthesia. It must be accepted that the technical difficulties involved in recording nerve action potentials are greater than those encountered in ordinary electromyography. The potentials to be recorded are much smaller, and therefore require higher amplification and more careful technique. With practice, however, the procedure is not more time-consuming than other electro-diagnostic tests, and if suitable apparatus is available there is nothing inherently impossible in its use as a routine diagnostic procedure.

Summary

The digital nerves in the fingers have been stimulated electrically with single shocks and the action potential of the afferent volley recorded through surface electrodes placed over the median and ulnar nerve trunks just above the wrist.

Sensory action potentials from the fingers were recorded from a large number of healthy median and ulnar nerves. Sixty-seven control observations were made, an action potential being recorded successfully in every case.

Forty-one patients with suspected median and ulnar nerve lesions were examined. In 13 patients, no sensory action potential could be recorded from the affected nerve when the appropriate finger was stimulated. In other patients, the recorded action potentials were of small amplitude and long latency when compared with the control group.

Two patients had brachial plexus lesions causing sensory loss in the hand. In neither of them could a sensory action potential be recorded from the wrist when an affected finger was stimulated.

Seven patients with chronic polyneuritis and two with peroneal muscular atrophy were examined. Sensory action potentials were small and delayed in two cases and absent in the remainder.

It is concluded that the technique can be of practical value in the investigation of patients with sensory disorders affecting the upper limbs.

We wish to thank members of the staff of the National Hospital who have referred patients for investigation. We also wish to thank Dr. G. D. Dawson and Dr. W. A. Cobb for helpful criticism and advice, and Mr. H. B. Morton for technical assistance.

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THE PSYCHO-GALVANIC REFLEX

A COMPARISON OF A.C. SKIN RESISTANCE AND SKIN POTENTIAL CHANGES

BY

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Two closely-related electro-dermal phenomena constitute the so-called " psycho-galvanic reflex ". These are (*a*) a decrease in the electrical resistance of the skin, and (*b*) a change in the skin electromotive force in response to a wide variety of stimuli.

Féré (1888) connected two electrodes on the forearm of a subject in series with a weak source of electricity and a galvanometer. He observed that various sensory and emotional stimuli were associated with an increased deflection of the meter. Tarchanoff (1890) obtained similar deflections of a galvanometer without the aid of an external electromotive force.

Gildemeister (1923) found that the phenomena of Féré and of Tarchanoff possessed similar latent periods. Jeffress (1928) confirmed this, and he also obtained a high positive correlation between the magnitude of the two responses. These workers, like Tarchanoff, used an instrument of low resistance, which would not fully differentiate potential changes from resistive effects.

Forbes (1936) oscillographically recorded the pure potential and impedance changes of a single reacting area of skin. He reported the existence of two distinct components in the potential " waveform ", and he referred to the " slower resistance or impedance response ".

Goadby and Goadby (1949) found that the resistance response was abolished by complete exsanguination of a limb, while the potential response remained intact. They concluded that the resistance change was due to vasoconstriction and that the potential variations were probably expressions of activity at sympathetic nerve endings in blood vessels and sweat glands.

The object of this paper is to present the results of experiments in which the apparent A.C. resistance and the skin potential of a single reacting area were continuously recorded under a variety of conditions. The mutual independence of the two phenomena was repeatedly confirmed.

Methods

Material.—The subjects were 17 male and seven female patients who were suffering from various functional mental disorders. Their ages ranged from 16 to 58 years. Several of them were investigated on a number of occasions. Forty-six experiments were performed, during each of which the apparent A.C. skin resistance and the skin electromotive force were recorded for periods ranging from half an hour to more than one and a half hours.

Experimental Conditions.—The subject lay on a bed in a thermostatically heated room, the temperature of which was kept at 72 to 74° F. The equipment was in the adjacent room, from which the subject could be observed through a one-way screen of Venetian glass. During the first half hour the subject was encouraged to relax and was left undisturbed. Thereafter, various stimuli were applied. In six experiments the subjects slept spontaneously during the initial resting period; in three more cases sleep was induced with the help of a small dose of " seconal " by mouth. In the last 10 experiments the effects of certain drugs were studied after local application by iontophoresis.

A.C. Skin Resistance.—The subject was connected in series with 10 megohms to a stabilized 60-cycle source of 2 volts peak. The current of 0·2 μA. was therefore virtually constant over the whole range of recorded resistance values. A frequency of 60 c.p.s. was chosen in order to eliminate the beats which resulted from a small amount of 50-cycle interference when the oscillator was set at this frequency. The voltage developed across the electrodes was amplified, rectified, and compared with a constant reference voltage. At the beginning of the experiment the signal was balanced against the reference by adjusting the gain of the amplifier until the null point was obtained on a centre-zero meter. A decade box was substituted in place of the subject, and the instrument was adjusted to balance at the nearest convenient figure. This was the " reference level " for the experiment, and any departure from it was indicated in terms of percentage change. Two ranges of sensitivity provided full-scale deflection for changes of $\pm$ 50% and $\pm$ 25% of the reference value, and these ranges were linear to within $\pm$ 1% of full scale. In practice, the less sensitive range was nearly always used. The instrument was arranged to cut out if full-scale deflection was

exceeded in order to protect the recording device in the event of an electrode being displaced.

Skin Potential.—A two-stage balanced D.C. amplifier was used. Since one electrode was at earth potential, the instrument was operated asymmetrically and the second input grid was grounded. The input resistance was 10 megohms and the grid current was negligible. Two ranges of sensitivity gave full-scale deflection for 50 mV. and 100 mV., and these ranges were linear to within ± 1%.

Mutual Independence of the Measures.—Both measures were recorded simultaneously through the same pair of electrodes, the active electrode being condenser-coupled both to the A.C. source and the A.C. amplifier. To determine whether the applied A.C. had any undesirable effect on the potential measurements, a 100,000 ohm resistor was connected in place of the subject. It was found to be necessary to multiply the A.C. current 10 times in order to produce a deflection corresponding to 0·5 mV.

Electrodes.—These consisted of fine silver discs, 1 cm. in diameter, which were recessed in shallow polythene cups. The discs were chlorided electrolytically, and the cups were filled with a jelly which consisted of starch, glycerine, and sodium chloride (*vide infra*). Two electrodes with less than 1 mV. difference in potential were selected, and this difference in potential was checked at the beginning and end of every experiment.

Location of Electrodes.—The active electrode was attached by adhesive tape to the palmar surface of the tip of the right middle finger. The skin at this site was not prepared in any way in order to minimize the disturbance of the normal conditions. The earthed electrode was attached, also by adhesive tape, over the forearm extensors of the same side. To make this area as unreactive as possible the skin was rubbed briskly with ether and was pierced with a hypodermic needle. A drop of blood was squeezed to the surface and electrode jelly was rubbed well in. To show that this area was truly inactive, three subjects were treated as follows: At the end of an experiment the active electrode was transferred from the tip of the finger to the mucous membrane of the lower lip. In each case the resistance fell from above 10,000 ohms to less than 1,600 ohms, and measurable responses could not be elicited. (The current was increased tenfold in order to make the measurements.) The electromotive force also decreased, and reactions to stimuli were unobtainable.

Recording Instruments.—Two similar "record" 0 to 1 mA. pen recorders were used, one of them being modified for centre zero operation. The chart rulings were aligned at the start of each experiment and were used as time marks. A chart speed of ½ inch per minute was usual, but in some cases further detail was obtained by increasing this to 1 inch or 3 inches per minute. Provision was made for inserting synchronous signal marks on each trace, but since these marks tended to obscure the traces at slow paper speeds, they were only used for demonstrating alignment of the rulings. Stimuli were usually applied as the pens crossed a line.

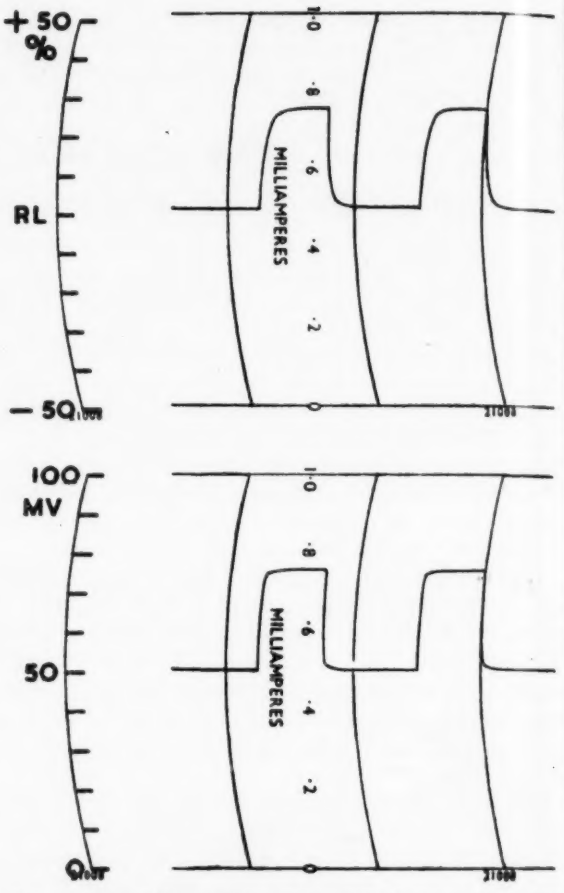

FIG. 1.—The relative response times of the instruments to simultaneous abrupt changes of input.
Upper trace shows resistance (reference level = 30,000 ohms); lower trace shows potential difference.
Time scale: rules at 20-second intervals.
The scales shown on the left are applicable to all the illustrations.
RL = Reference level.

Response Time.—The two recorders were damped unequally by their associated circuits. The responsiveness of the instruments was therefore studied by simultaneously changing the electromotive force and the resistance of a simple skin analogue. The results are reproduced in Fig. 1, which shows a greater lag in the resistance trace.

Stimuli.—Four types of stimuli were used: (*a*) A rapid, make-and-break shock from a high tension battery through two electrodes on the calf of one leg. The intensity of the shock was preliminarily adjusted until the subject stated that it was slightly unpleasant; (*b*) a variety of auditory stimuli from a loudspeaker under the bed; (*c*) a cough or deep breath; (*d*) a hypodermic "injection".

Drugs.—The local effects of the following drugs were studied by means of iontophoresis:—(*a*) Atropine sulphate, 3% solution, (four subjects); (*b*) eserine salicylate, approximately 1% solution (three subjects); (*c*) mecholyl

chloride, 0·5% and 1% solutions (three subjects). In each case the drug was introduced from the positive pole with a current of 3 mA. for a period of 10 minutes. Three control tests were made with water under otherwise similar conditions.

In these experiments a second active electrode was attached to the palmar surface of the left mid finger, which was used as a control. The recording instruments were switched from side to side at approximately three-minute intervals. After a preliminary period of half an hour, in which it was ascertained that both sides were reacting similarly to stimuli, the active electrodes were removed. The right mid finger was placed in the solution of the drug, and the fingers of the opposite hand were immersed in a bowl of water, which formed the dispersive electrode. After the treatment both hands were dipped into warm water for a few seconds and they were dried by dabbing with a towel. The electrodes were reapplied and a warm pad was wrapped round each mid finger.

Results

Slow Changes.—During the initial period of quiet rest the skin resistance nearly always showed a steady tendency to fall. In the case of the potential the active electrode was always found to be negative with reference to the inactive electrode, and the potential difference showed less tendency to drift. In all but three of the experiments the initial value of the resistance was also the highest value recorded during the test, and in the exceptional cases the resistance remained near the initial level. In no case did it show an upward trend. The drop was occasionally marked, the resistance falling to less than half of the initial value within 15 minutes. It tended to rise again in association with anticipation and alertness when the subject was disturbed. The potential difference, on the other hand, fluctuated about a steady level in half of the cases; in the other half it sometimes rose and sometimes fell.

The consistent tendency displayed by the resistance to decrease during a period of rest was contrary to previous experience with the same instrument under similar conditions. In a series of more than 200 recordings the skin resistance had usually shown a progressive upward trend, which was sometimes marked. In those cases, however, the active electrode had consisted of a flat disc with an intervening square of paper moistened with normal saline. It seemed probable that the decreasing resistance in the present studies was associated with the use of an electrode jelly. On enquiry, this was found to contain as much as 25% of sodium chloride. The supposition was confirmed by including three subjects in both series, when the appropriate opposite trends were observed in every case. Nevertheless, in view of some interesting findings which were associated with the progressive decline in the resistance level, the hypertonic jelly was retained throughout the present tests.

Rapid Changes.—Many of the more rapid fluctuations in the measures were provoked by deliberate or incidental stimuli. Other similar changes frequently appeared in the absence of any identified cause, and there seemed to be no qualitative differences between the spontaneous and the induced activity. However, a stimulus if effective was always followed by a change in both resistance and potential, a relationship which was not always evident in the case of spontaneous fluctuations. This will be referred to again later.

Although an induced response in one measure was invariably accompanied by a change in the other, the sizes and forms of the two phenomena were seen to vary independently. With the exception mentioned below the resistance responses were consistent in form. Each response comprised a sharp fall in resistance, which was followed by a slower return toward the base line, as seen in Fig. 2. On the other hand, the rapid changes in potential appeared less consistent and four distinct forms were noted: (*a*) A simple increase in the potential difference; (*b*) a small decrease followed by a larger increase; (*c*) a small increase followed by a larger decrease; and (*d*) a simple drop in potential difference. Various complex polyphasic forms were also noted, but after comparison with the corresponding resistance changes it seemed probable that these contained several component responses. Falls in potential difference were seen to be more rapid than rises, and each was usually followed by a proportionately slower return in the appropriate direction toward the base line. At the usual paper speed of ½ inch per minute, increases in potential difference appeared characteristically humped (Fig. 2); decreases were often more angular (Fig. 4). When several falls occurred consecutively, the similarity of the potential and resistance traces was sometimes striking.

Owing to the use of a hypertonic electrode medium the resistance showed a slow tendency to decrease, as already described, when the subject was left undisturbed, and to rise again when he was alerted. Consequently, it was possible to observe the effects of stimulation at various levels of the base line. It was noted that after a period of rest in which the base line decreased the additional drop in resistance in response to a stimulus was often disproportionately small but that the resistance subsequently regressed to a higher level. Succeeding stimuli evoked larger responses, which tended to bring the resistance down to, but not below, the level of response to the first stimulus. This trend may be

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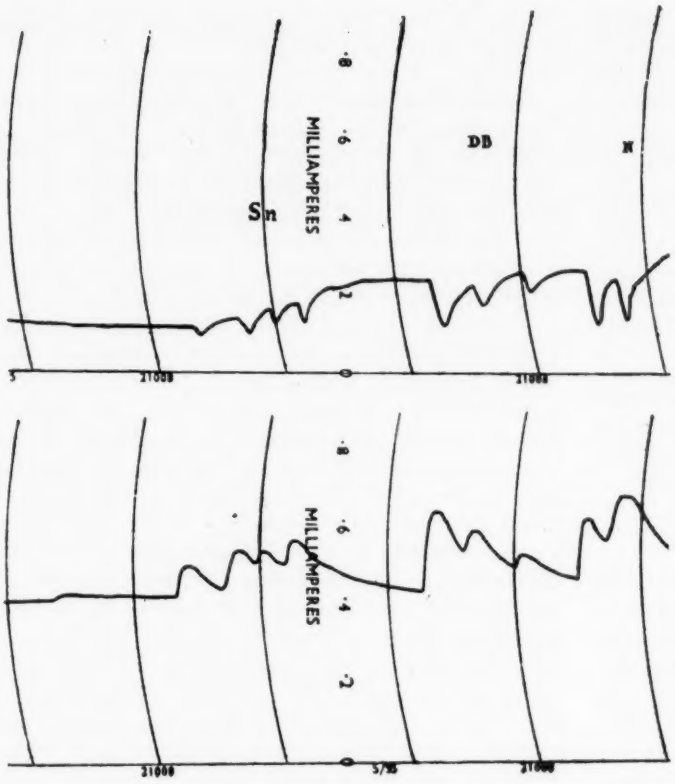

FIG. 2

FIG. 2.—Responses to repetitive incidental stimuli after a period of rest.

The stimuli were identified as sniffs (Sn), deep breaths (DB), and a noise (N).

Upper trace shows resistance (reference level = 16,000 ohms); lower trace shows potential difference (active electrode negative).

Time scale: rules at 2-minute intervals.

FIG. 3.—Responses obtained on arousal of a sleeping subject. Note the absence of a further drop in resistance.

Upper trace shows resistance (reference level = 16,000 ohms); lower trace shows potential difference (active electrode negative).

Time scale: rules at 2-minute intervals.

Arrows denote approximate point of entry into subject's room.

seen in Fig. 2. In such cases even strong and repetitive stimuli failed to bring the resistance down below the apparent minimal value, but the subsequent " overshoot " was greater.

The question of whether the base line would ever reach the minimal level was answered when a subject fell asleep spontaneously soon after the start of an experiment. This was accompanied by a steady exponential decrease in resistance to 39% of the initial value during the ensuing half hour. When the subject was aroused at the end of this period, there was no further drop in resistance but only a large and rapid rise, which began after a longer latent period than the corresponding potential response. This reaction is illustrated in Fig. 3. Several more attempts to confirm this observation were partially successful. Eight other subjects were encouraged to go to sleep either spontaneously or with the help of a small dose of " seconal " by mouth. On three of these occasions this was accompanied by a slow decrease in resistance to values of less than 18,000 ohms, and in each case abrupt awakening of the subject caused only a slight or imperceptible additional drop in resistance (mean drop of 500 ohms), which was followed by a large rise. In the remaining cases there occurred a smaller

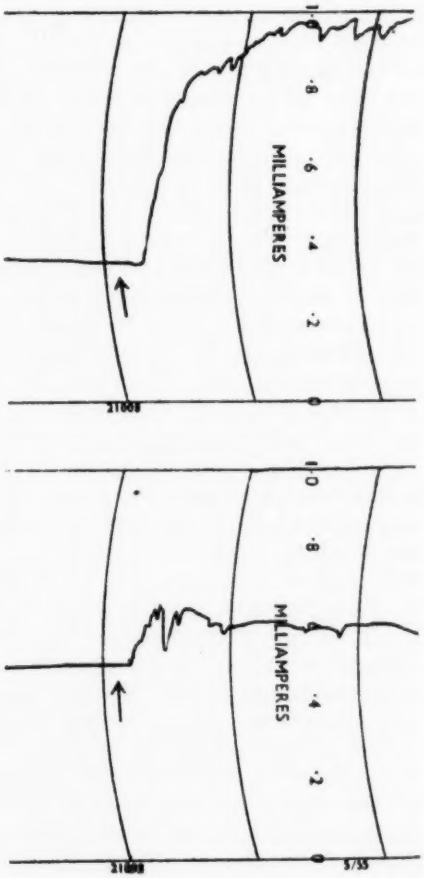

FIG. 3

decline in resistance during sleep to values above 19,000 ohms. Arousal of these subjects evoked a mean additional drop of 5,500 ohms and the subsequent overshoot was less evident or did not exist. This variation in the size and character of the resistance changes was not associated with any similar pattern in the corresponding potential responses.

The different forms of potential response assumed greater significance when they were studied in relation to their base lines. It was then found that if the potential difference was low it tended to increase, and that decreases occurred when the potential difference was already high. This was well illustrated in a few tests in which the potential difference showed a slow decline, punctuated by spontaneous fluctuations, as the subject relaxed. In such cases a complete transition in the form of the fluctuations was sometimes observed. Initial falls were succeeded by biphasic changes and ultimately by pure rises. Falls reappeared whenever the potential difference approached a certain value, which remained approximately constant in any particular test. In consequence, the potential difference was prevented from exceeding an apparent limit regardless of the size of the disturbances. The operating range varied considerably from case to case, the highest and lowest values differing by as little as 11 mV. in one test and by more than 40 mV. in five others. In the last few experiments the responses in the two hands were compared by switching from one to the other, and an initial inequality was sometimes observed in the potential levels on the two sides. There was also some evidence that this could be associated with different forms of response, the potential difference falling in the finger with the highest potential and *vice versa*. As the subject adapted to the environment the discrepancy in the levels diminished progressively and the responses became similar in form and magnitude.

Traces which illustrate some of these points are reproduced in Figs. 4 to 6. In Fig. 4 the first stimulus, a shock, evoked a large increase in the potential difference. The flat plateau which may be

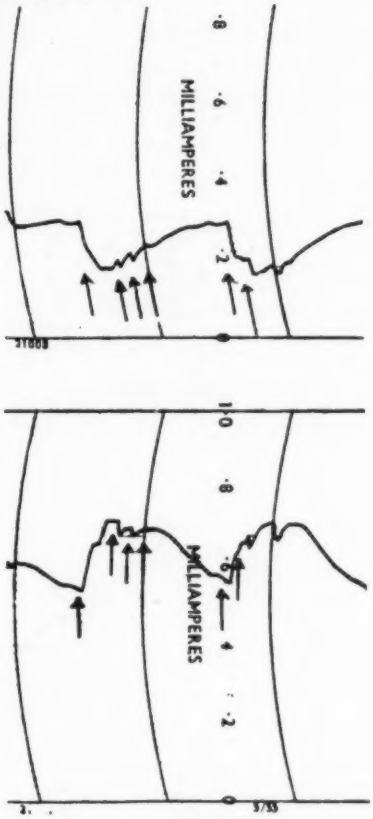

FIG. 4

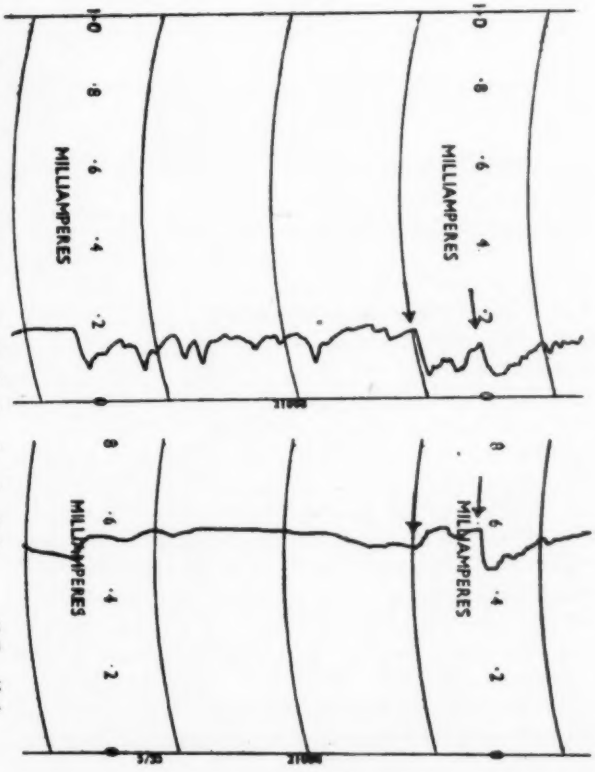

FIG. 5

FIG. 4.—Traces illustrating various forms of potential response. Note the plateau at the peak of response to the first stimulus.
Upper trace shows resistance (reference level = 30,000 ohms); lower trace shows potential difference (active electrode negative).
Time scale: rules at 2-minute intervals.
Arrows denote electric shocks.

FIG. 5.—Traces illustrating dissimilarities in spontaneous activity in the two measures. The potential response to the second stimulus is inverted.
Upper trace shows resistance (reference level = 20,000 ohms); lower trace shows potential difference (active electrode negative).
Time scale: rules at 2-minute intervals.
Arrows denote auditory stimuli.

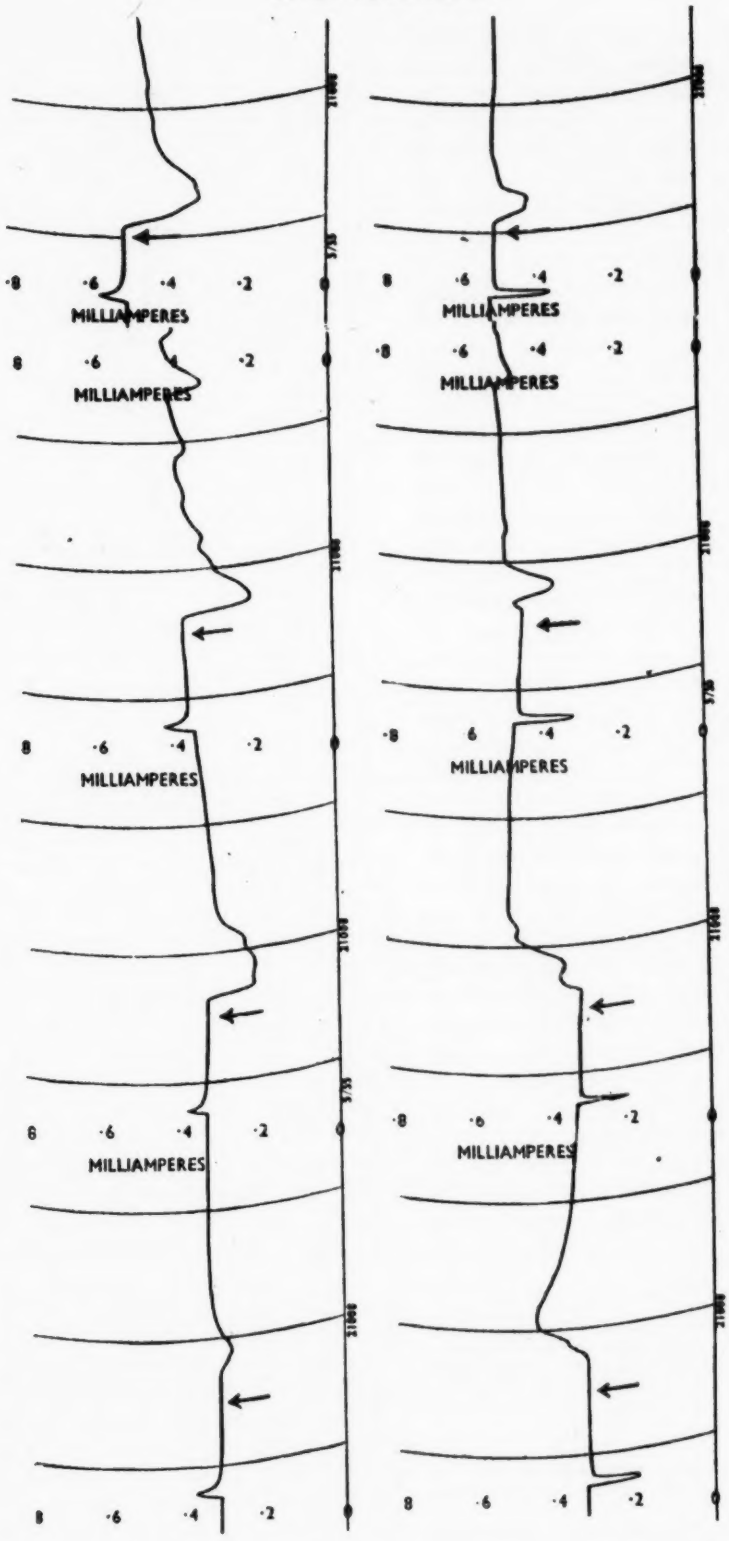

FIG. 6.—Series of responses showing transition from rise to fall in potential difference.
Upper trace shows resistance (reference level = 30,000 ohms); lower trace shows potential difference (active electrode negative).
Time scale: rules at 20-second intervals.
Arrows denote auditory stimuli.
Signal marks before the arrows indicate alignment of the charts.

seen at the peak of this response is of interest since the level of 72 mV. was the highest value to be recorded during the experiment. Furthermore, the potential difference reached this point on seven occasions during the course of half an hour. The two succeeding shocks were given while the potential difference was still raised to this level, and each evoked a fall. A similar inversion of response to a second stimulus may be seen in Fig. 5, and in this case the drop terminates in a plateau. This was the lowest point to be attained in this recording. The last stimulus in Fig. 4 was applied when the potential difference was submaximal and it induced a small biphasic response. The consecutive series of responses which is shown in Fig. 6 illustrates in greater detail a transition from increase to decrease in potential difference through an intermediate biphasic stage with successive stimulation.

It was evident from these observations that the size of the resistance drop and the form of the potential response were related to their respective base lines. Since there was no consistent association between the slow changes in resistance and potential, there was also no apparent relationship between the two responses apart from their concurrence. In Fig. 3 a large potential change was accompanied by a rise in resistance without any preliminary drop. Elsewhere, the various forms of potential response were each associated with a decrease in resistance. It is also interesting to note that a biphasic potential change was accompanied by a single drop in resistance, as seen after the third stimulus in Fig. 6. In their time relations the two phenomena generally exhibited similar latent periods. When any discrepancy was observed, the resistance change invariably appeared to lead, but slow paper speeds made the traces unconvincing. A more detailed example is shown in Fig. 7, in which similarity of latency is indicated by a barely perceptible initial change in potential; in other respects temporal differences are evident. Nevertheless, every effective applied stimulus was followed by a change in both resistance and potential. In the case of spontaneous fluctuations, on the other hand, even this relationship was not always apparent. A considerable amount of activity can be seen in the resistance trace of Fig. 5, but much of this is unaccompanied by any perceptible change in the potential. Yet the applied stimuli evoked deflections in both traces of approximately equal magnitude.

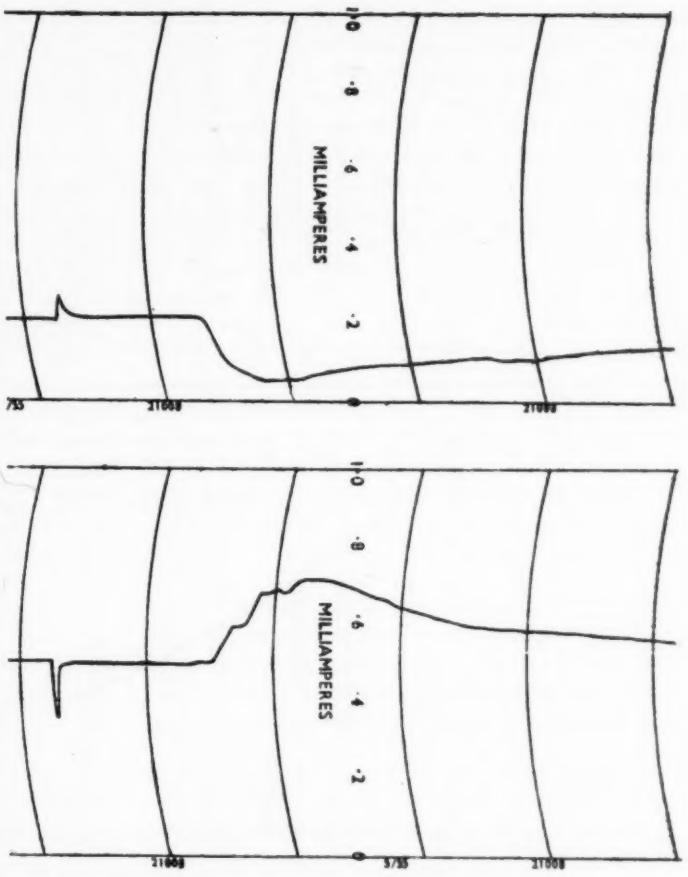

FIG. 7.—Responses to a deep breath showing dissimilar temporal relations.
Upper trace shows resistance (reference level = 20,000 ohms); lower trace shows potential difference (active electrode negative).
Time scale: rules at 20-second intervals.
Signal marks on extreme left confirm correct alignment of charts.

The evidence that has been advanced so far indicated that the two phenomena were dependent, in part at any rate, upon different peripheral mechanisms since they varied independently in accordance with local conditions. However, their concurrence in response to stimuli suggested that, with the possible exception of some spontaneous changes in resistance, the phenomena might be mediated through the same nervous pathway. It was therefore decided to study the effect of atropine on the responses in order to determine the part played by the cholinergic fibres of the sympathetic supply to the skin. Atropine was applied locally to the right mid finger by iontophoresis, while the corresponding finger of the left hand was used as a control. The latter was included in the dispersive area at the negative pole during iontophoresis. It

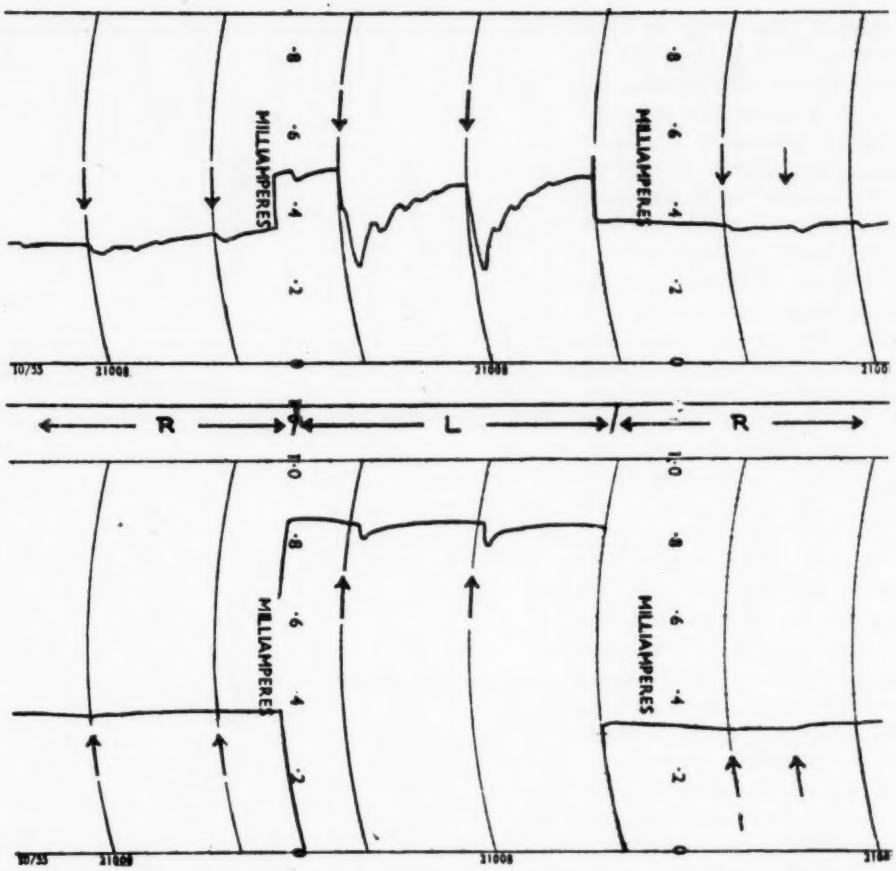

FIG. 8.—Comparison of resistance and potential responses on the right and left sides 15 minutes after local atropinization of the right mid-finger.
Upper trace shows resistances reference level = 30,000 ohms); lower trace shows potential differences (active electrodes negative).
Time scale: rules at 1-minute intervals.
Arrows denote alternate deep breaths and coughs.

soon became apparent that some of the effects were due to the electric current *per se*, and a control procedure with water at both poles was therefore used on three occasions. The effects of the galvanic current were then found to be as follows:—

(*a*) The negative potential in the right finger (positive pole) was always found to be reduced, and that on the left side increased, when recording was resumed after galvanization. The drop on the right side ranged from 10 to 70 mV.; in one case the finger was still 10 mV. positive with respect to the inactive electrode. On the left the potential was invariably raised above 90 mV., the increase ranging from 15 to 50 mV. The potentials on the two sides gradually returned towards the common initial level but there was always a considerable residual discrepancy at the end of the experiment.

(*b*) The potential responses were greatly reduced on both sides, and in one case no perceptible changes could be elicited for 10 minutes. The responses gradually increased on both sides equally, but even after 30 to 40 minutes they had seldom attained their initial magnitude. It was also noted that the responses sometimes, although not invariably, assumed different forms on the two sides in association with the dissimilar potential levels. When this occurred, increases in potential difference were recorded from the right side and decreases from the left.

(*c*) The galvanic current caused no consistent change in the level of the skin resistance. This was either the same as, or lower than, the pre-treatment value, and any decrease that occurred was approximately equal on both sides. It seems probable that this variable reduction may have been due to the precautions which were taken to ensure adequate and equal local temperatures.

(*d*) The bilateral equality of the resistance responses was unaffected by the current.

When atropine was introduced from the positive pole several additional effects were obtained. In two of the four subjects atropinization was followed by a moderate increase in the level of the skin resistance on the treated side only; in the remaining cases there was little change. The other effects were quite consistent. After a period which varied from five to 15 minutes a progressive diminution was noticed in the resistance responses on the treated side. In three of the subjects no responses at all could be elicited after periods of 10, 15, and 30 minutes respectively; in the fourth case the responses were scarcely perceptible after 25 minutes when the experiment was terminated. The results in this last case can be seen in Fig. 8, which shows a marked difference in the responses on the two sides 15 minutes after iontophoresis. The effect on the potential responses was similar, although more rapid. In every case responses were abolished on the treated side within five to 15 minutes; in the opposite finger, on the other hand, the responses gradually increased in size, as in the control tests.

Since atropine was found to abolish the responses it was considered that it would be of interest to find out whether they would also be potentiated by eserine. This was found not to be the case. In only one subject was there any apparent difference between the two sides in the half hour following iontophoresis. On this occasion the resistance changes in the control finger were nearly three times as large as on the treated side for 15 minutes, after which they rapidly diminished to equality.

Finally, the effect of acetyl β-methylcholine (mecholyl) was studied in order to see if the responses could be reduced or abolished by inducing an excessive local acetylcholinomimetic action. This also was unaccompanied by any significant change in the resistance level, and neither the resistance nor the potential responses showed any consistent differences between the two sides.

Discussion

Under normal conditions an applied stimulus, if effective, was always followed by a change in both resistance and potential. However, the forms of the two responses altered independently, and their concurrence was not invariable in the case of spontaneous activity. It seems that they are dependent, in part at any rate, upon different mechanisms. The resistance change has been shown by other workers to be either considerably reduced (Carmichael, Honeyman, Kolb, and Stewart, 1941) or completely abolished (Goadby and Goadby, 1949) by exsanguination of the part. This procedure did not alter the potential response (Goadby and Goadby, 1949). The segregation of the two phenomena has now been carried a step further by finding that the potential response was reduced or absent after passing a galvanic current through the skin, and that this did not affect the resistance change. By means of an appropriate alteration of the local conditions either response may be reduced or abolished independently of the other. Their dependence upon separate mechanisms is an inevitable conclusion.

Forbes (1936) claimed to have demonstrated a predictable potential " waveform " from a single reacting area of skin. This comprised a negative " a " potential followed by a positive " b " potential, the latter being apparently dependent on an intense stimulus or on apprehension. Forbes studied these changes without reference to the base line. Although his finding has been confirmed, it now appears that the form which he described constitutes a special case which only occurs at an intermediate level of activation. A decrease in potential difference (Forbes' " positive " component) has sometimes been seen to precede an increase, and both increases and decreases occur independently in association with lower and higher initial potential differences respectively. There was nothing in the present recordings to suggest that the two components of a biphasic response were each associated with a separate release of mediator, as Forbes (1936) believed. Such responses were accompanied by a single change in resistance. Moreover, there was some evidence to suggest that different forms of potential response may occur simultaneously in the two hands when the local conditions are different. The exact form assumed by any response appeared to be determined by the magnitude of the disturbance and by the existing local conditions.

The resistance response is believed to be largely or entirely due to vasoconstriction (Carmichael *et al.*, 1941; Goadby and Goadby, 1949). That there is no evidence of dilator fibres in the digits has been re-emphasized by Ackner and Pampiglione (1957), who also state that " the degree of the reduction of volume following a stimulus is partly related to the pre-existing dilatation and no reflex vasoconstriction can be expected if the vessels are not adequately dilated at the time ". This observation is closely parallelled in the present study by the virtual disappearance of the resistance response as the base line approached an apparent minimal value. The slow, pronounced decline in resistance which brought this point to light occurred when the subjects relaxed or fell asleep. That the skin resistance should fall during sleep is contrary to general experience (see Woodworth and Schlosberg, 1955) as well as to previous observations with the same instrument. It was found to be associated with the use of a strongly hypertonic electrode jelly, and it would be of in-

terest to know whether this was also accompanied by vasoconstriction. The mechanism whereby the resistance returned to a higher level after stimulation despite the persisting presence of the jelly is likewise unclear.

Earlier reports concerning the effects of atropinization have been well reviewed by Landis and DeWick (1929), and they are seen to be utterly conflicting. More recently, Carmichael *et al.* (1941) have reported that the resistance response was consistently found to persist after localized atropinization by iontrophoresis. The same technique was used in the present study but with opposite results. The resistance and the potential changes were both consistently abolished, the latter being the first to disappear. In the control finger, on the other hand, the resistance responses remained undiminished and the potential changes gradually increased. These conflicting findings are hard to explain, The positive results that were obtained in the present instance with atropine suggested that the responses might also be affected by eserine and by acetyl β-methylcholine, but this was found not to be the case. The negative outcome of these trials is of little significance since there was no certainty that an adequate local concentration of the drugs had been achieved.

The dependence of both the resistance and the potential response upon an intact sympathetic innervation has been amply demonstrated in the past (Schilf and Schuberth, 1922; Richter, 1927; Wang and Richter, 1928; Carmichael *et al.*, 1941; Goadby and Goadby, 1949). The present results with atropine suggest that both phenomena are also cholinergically mediated.

Summary

The apparent A.C. skin resistance and the skin potential of a single reacting area were continuously and simultaneously recorded under a variety of conditions.

The use of a strongly hypertonic electrode jelly was associated with a progressive decrease in the skin resistance, which was further enhanced during rest and sleep. Stimulation under these conditions evoked a negligible additional drop in resistance but caused it to return to a higher level. Subsequent stimuli evoked larger falls.

The active electrode was always found to be negative with respect to the inactive area. The form of the potential response was seen to be related to the initial potential difference. When this was low, stimulation caused it to increase; decreases occurred when the potential difference was high. At intermediate levels biphasic responses occurred. Decreases reappeared whenever the potential difference approached an apparent maximal value, which remained approximately constant in any particular test.

The resistance and potential responses varied independently in form and magnitude in association with their respective base lines.

" Spontaneous " fluctuations in resistance, which resembled responses to stimuli, occurred in the absence of any perceptible changes in skin potential.

The potential response was reduced or absent after a galvanic current had been passed through the skin. This procedure did not affect the resistance response.

The local application of atropine by iontophoresis resulted in the disappearance of both resistance and potential responses, which could still be elicited in a control finger.

It is concluded that the two phenomena are dependent upon different mechanisms. The effects of atropine suggest that both are cholinergically mediated.

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CLINICAL ASPECTS OF SUSCEPTIBILITY TO METHYLPENTYNOL

BY

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Methylpentynol (" oblivon "), one of the vinylethynl carbinols, was introduced into therapeutics by Margolin, Perlman, Villani, and McGavack (1951). Sears (1956) describes it as an important sedative producing mental relaxation and diminution of anxiety. The interest of the substance resides in the fact that not only is it an alcohol used therapeutically, but it is said to behave dissimilarly to the lower alcohols in that it is rapidly metabolized and is not cumulative in effect (Perlman and Johnson, 1952). The clinical evidence presented here argues against this and accumulation in animals has now been demonstrated by Marley and Vane (1958).

Preliminary investigations suggested that methylpentynol was less noxious than the barbiturates, a supposition modified by Goodman and Gilman (1955) who considered it more potent for man than for animals. Even so, early reports were unanimous in emphasizing the drug's paucity of toxic complications (Allen and Krongold, 1951; Hirsh and Orsinger, 1952; Malone, Klimkiewicz, and Gribetz, 1952) and human subjects have received 0·1 to 1·5 g. daily for six months without presenting undesirable side-effects (Chevalley, Heminway, Meyer, Frankhauser, and McGavack, 1952).

Recently, however, a number of dissentient publications have drawn attention to the drug's potential toxicity. Schaffarzick and Brown (1952) reported that two of six epileptics prescribed the substance developed a positive cephalin flocculation test. May and Ebaugh (1953) noted drowsiness, ataxia, and slurred speech in five patients who had ingested between 3·89 and 10·16 g. of methylpentynol during periods from two to six days. Glatt (1955) and Marley (1955) reported toxic sequelae from abuse of the drug, while Lovelace and Roith (1955) documented an attempted suicide with a combination of methylpentynol and " persomnia " (carbromal and bromvaletone). A death after a dose of 4·5 to 6·0 g. was confirmed by Cares, Newman, and Mauceri (1953) and another following the absorption of 2·25 g. of methylpentynol with 20 pentobarbitone sodium (" nembutal ") capsules (*British Medical Journal*, 1955).

Marley and Chambers (1956) were struck by the similarity between alcohol, barbiturate, and methylpentynol intoxications, and by the apparently small precipitating dose of the latter substance. While much information is available relating to the therapeutic applications of the drug (Bockner, 1957; Bourne, 1954; Gusterson, 1955; Simmons, 1954; Simpson, 1954; Trotter, 1953), little is known as to its limitations or contraindications, although Lasagna (1954) noted that its hypnotic effect (0·5 to 1 g. doses) was indistinguishable from placebo. A maximum of 2 g. a day has been suggested for sedation, although this might now seem too high. Sargant (1956) has justifiably inveighed against the prescription of a standard dose irrespective of the circumstances, for this ignores the inherent individual variability that influences the parameter of drug dosage and response.

Such a topic is far from banal, and medico-legal implications in connexion with an abnormal response to methylpentynol have been discussed elsewhere (*Lancet*, 1955). It was therefore deemed worth while to ascertain more exactly the clinical response to methylpentynol as distinct from its purely therapeutic effect.

METHODS

Fifty-four individuals (24 males, 30 females) aged 18 to 60 years were prescribed 0·5 g. q.d.s. of methylpentynol daily for five days, a base line of individual reaction being obtained by the immediate prior administration for the same period of an identical number of inert capsules. The subjects were informed that they would receive a drug from which they might or might not derive benefit and that each would be interviewed daily. Neither they nor the nursing staff were aware that inert capsules were being prescribed. An electro-encephalogram was obtained on the fifth day of the course of inert capsules (control E.E.G.) and again on the final day of the drug régime (drug E.E.G.). Of the 54 subjects, 18 were normal volunteers, and the remainder were in hospital

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with psychiatric disorders presenting anxiety or tension (neuroses or psychosomatic illnesses). Patients with factors likely to modify the response to drugs, such as a history of drug addiction, head injury, or hepatic or renal impairment, were excluded from the series.

The particular dose of methylpentynol chosen is the maximum recommended for sedation, and the five-day period of study was selected as it was anticipated to be too brief for either accumulation of the drug or for exposing anything but maximum susceptibility to the substance. The clinical response to methylpentynol was graded into three categories, the unexpected and considerable incidence of toxic phenomena determining a classification. Depending on the presence or absence of abnormal signs in the central nervous system, the categories were designated none, minimal, and maximal toxic. In a few individuals there were marked behavioural changes without abnormal signs, apparently attributable to a toxic effect of the drug. The clinical rating in these subjects depended on the degree of disturbance seen in the electro-encephalogram. (Our use of the word "toxic" requires amplification, inasmuch as it has been applied to undesirable side-effects produced by the drug. Robson and Keele (1951) refer to two main types of toxic effect arising during the administration of drugs. These are those ascribable to overdosage or to either idiosyncrasy or hypersensitivity. In our series, the toxic response was probably due to a combination of individual hypersensitivity with overdosage, 2 g. a day being too high for universal administration.)

The prototypes of clinical response to methylpentynol are as follows:—

A maximal toxic reaction (clinical grading 3) included most of the following:—Dilated pupils reacting sluggishly to stimuli, suffusion of the conjunctivae, sustained nystagmus on conjugate lateral gaze, diminished corneal reflexes, diplopia, ptosis, loss of tone in the lower facial musculature, dysarthria, and fine tremor of the protruded tongue. Cerebellar ataxia might be found in the limbs or an admixture of this with posterior column type of ataxy. The specific cerebellar features included intention tremor, dysdiadokokinesis, and dysmetria. Muscular hypotonia with diminished deep reflexes was also noted. Alteration in the mental state included distortion of mood, behaviour anomalies, impairment of attention, concentration, and abstract thought.

A minimal toxic reaction (clinical grading 2) was epitomized by little more than nystagmus on conjugate lateral gaze and slight unsteadiness of gait or drowsiness. Alterations of mood were also evident.

The designation of no toxicity (clinical grading 1) is self explanatory.

The presentation of the mental state is based on the method of examination used at the Maudsley Hospital. Bonnier's (1905) classification for body-image disturbance was used as was Lewis's definition of insight, that of a correct attitude to a morbid change in oneself (Lewis, 1934). As far as possible, the information relating to the mental status was quantified (Tables I-VII). In two of these (Tables V and VII) the significance of the results was determined by *t* tests for correlated data, while for another three (Tables III, V and VI) the results were assessed by an arc sine transformation, which is a statistical technique for analysis of small populations (Davies, 1954). In order that the transformations should be valid the raw data were rearranged into 2 × 2 contingency tables achieved by contrasting the proportion of individuals affected and not affected for the particular function under investigation, *e.g.*, mood change, impairment of retrospective memory, or subjective time alteration, falling into either clinical grading 1 or the combined clinical gradings 2 and 3.

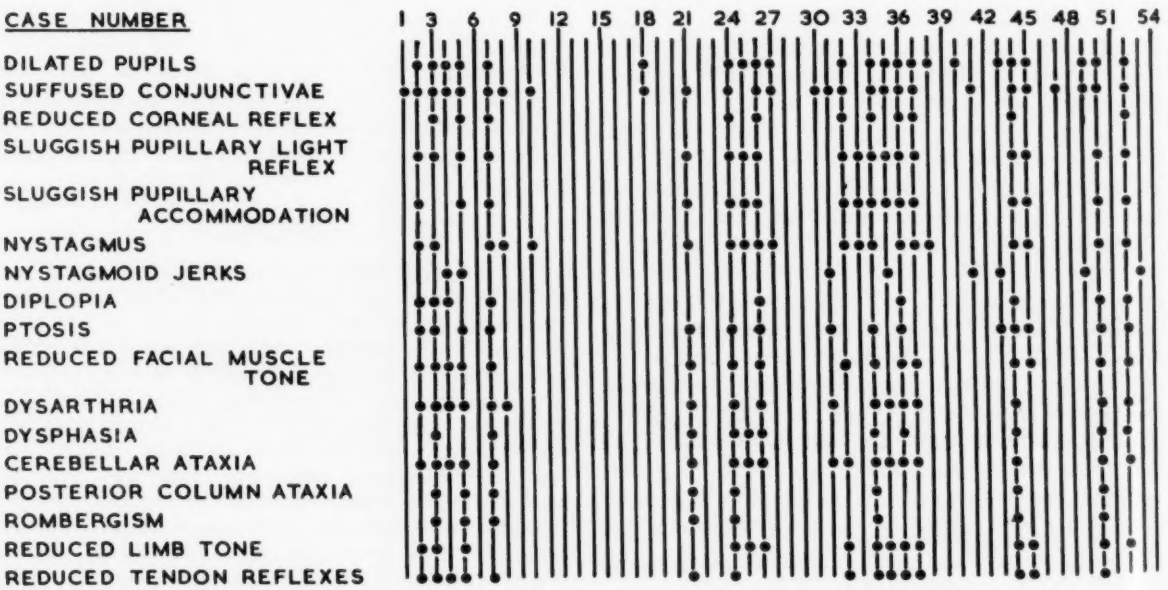

FIG. 1.—Abnormal physical signs seen in subjects given methylpentynol 0·5 g. q.d.s., for five days.

RESULTS

Of the 54 patients, 22 showed no reaction to methylpentynol, 15 developed minimal and 17 maximal toxic reactions. The abnormal physical signs encountered in patients manifesting susceptibility are depicted in Fig. 1.

Abnormal Physical Signs

Ocular Disorders.—Marked suffusion of the conjunctivae was noted in 27 subjects.

Alterations in pupil size were discovered in 23 patients, amounting to unequal pupillary dilatation in one (Case 52) and equal bilateral dilatation of the pupils in the 22 other affected individuals. These abnormalities were grouped with a spectrum of other physical changes except in two subjects (Cases 18, 40).

The light reflex was sluggish to both direct and consensual stimulation in 18 subjects, while that for reflex accommodation was impaired in 17.

The corneal reflex was reduced in 11 of the series, but only when accompanied by reduction of facial muscle tone (Cases 3, 5, 7, 24, 26, 32, 34, 36, 37, 44, 52) and in association with bilateral ptosis in all except two of the cases (Cases 32, 37).

In spite of the absence of paralytic strabismus or of any apparent disturbance of reflex conjugate lateral or vertical gaze, erroneous projection of the visual field was noted in nine patients. The diplopia was unilaterally or bilaterally uncrossed on lateral gaze for seven of the affected individuals and crossed for two others (Cases 26, 36). Diplopia on vertical gaze was seen in Case 52 only.

Sustained horizontal nystagmus on conjugate lateral deviation of the eyes was noted in 20 patients and unsustained nystagmoid jerks in a further eight individuals. Occasionally a small rotatory element to the nystagmus was evident.

Facial Musculature Tone.—Ptosis of the upper eyelids was seen in 15 subjects, together with, in 13 of these, a symmetrical loss of tone of the lower face musculature (Fig. 2). The ptosis might be unilateral or bilateral and was associated with overaction of the frontalis muscle. The drooping of the lid was slight, suggesting involvement of the orbital smooth muscle, but conjugate vertical elevation of the eyes was usually, although not invariably, unaccompanied by elevation of the upper lids. No actual weakness of the facial musculature was discovered.

Speech Disorders.—Seventeen patients became dysarthric while receiving methylpentynol. Mixed varieties of dysphasia compatible with a general disturbance of central nervous function was encountered in 11 individuals. This amounted in the mildest form to nominal dysphasia with the patient failing to name unfamiliar objects and without resort to periphrasis. In more severe instances, dysprosody, paragrammatism, and even paraphasia developed (Cases 3, 21, 32). Comprehension of spoken speech was normal, and no dyspraxic or gnostic difficulties emerged.

(*A*) (*B*)

FIG. 2.—Loss of lower facial musculature tone in a subject with methylpentynol intoxication: (*A*) Control, (*B*) Receiving drug.

Tremor of the tongue was fine and rapid in character being elicited on protrusion of the tongue in 14 individuals (Cases 2, 4, 5, 21, 24, 26, 32, 34-36, 44, 49, 50, 52).

Trunk and Limbs.—Static tremor of the outstretched hands was found in 10 patients (Cases 2, 4, 5, 21, 31, 34, 44, 49, 50, 52).

No gross abnormality of the rapidity, strength, or range of active movements was encountered. Coordination was affected, and, of the 18 individuals becoming ataxic, 10 exhibited cerebellar features in pure culture (Cases 2, 4, 25, 26, 31, 32, 35-37, 52) and eight presented a picture of mixed cerebellar and posterior column ataxy. Of the specific abnormalities, intention tremor on the finger-nose and heel-toe tests not compensated for by vision and dysmetria was commonest. Dysdiadokokinesis was also seen. These disturbances occurred in the presence of other abnormalities, nystagmus or nystagmoid jerks being invariably present. Reduced limb tone was found in 15 of the patients.

A number of subjects complained of unsteadiness in the absence of any substantiating deficit. In severely affected cases, the abnormality of gait was obvious, the Romberg test being positive in eight such patients.

The deep reflexes were diminished in 15 subjects.

Mental State

The diagrammatic representation of the mental state (Fig. 3) has entailed simplification, and modalities unaffected by the drug, *e.g.*, orientation, have been omitted.

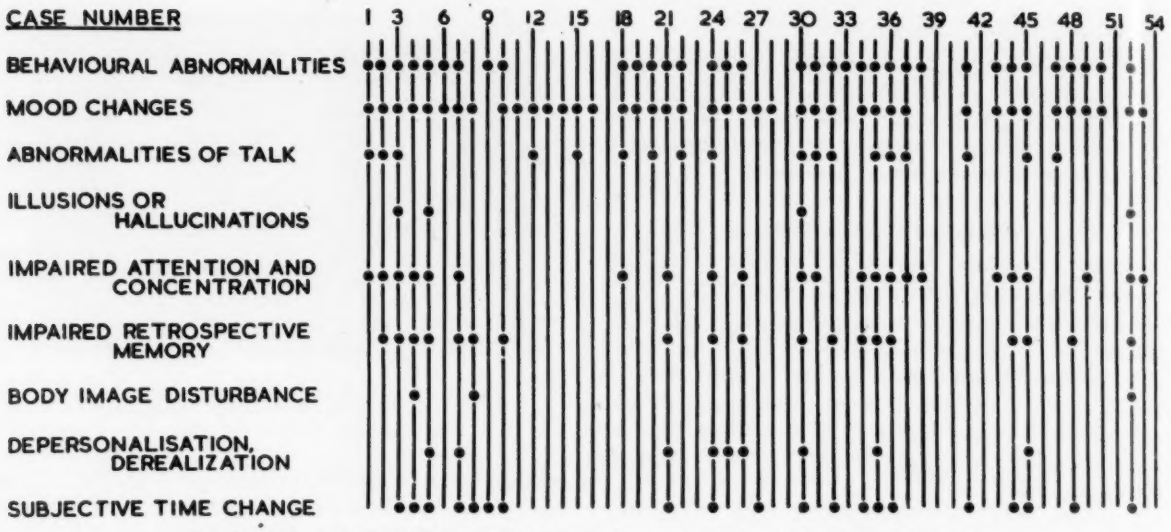
CASE NUMBER
1 3 6 9 12 15 18 21 24 27 30 33 36 39 42 45 48 51 54
BEHAVIOURAL ABNORMALITIES
MOOD CHANGES
ABNORMALITIES OF TALK
ILLUSIONS OR HALLUCINATIONS
IMPAIRED ATTENTION AND CONCENTRATION
IMPAIRED RETROSPECTIVE MEMORY
BODY IMAGE DISTURBANCE
DEPERSONALISATION, DEREALIZATION
SUBJECTIVE TIME CHANGE

FIG. 3.—Abnormal mental phenomena in subjects given methylpentynol, 0·5 g. q.d.s., for five days.

General Behaviour.—This is exemplified in the four adjectival subdivisions, normal, drowsy, overactive, and aggressive, although no behavioural spectrum could be codified adequately in this restricted fashion. Details are presented in Table I.

TABLE I

DISTRIBUTION OF BEHAVIOUR PATTERNS RELATED TO CLINICAL RESPONSE TO METHYLPENTYNOL

Behaviour	Clinical Grading		
	1	2	3
Normal	16	3	0
Drowsy	1	10	13
Overactive	3	0	2
Aggressive	2	2	2

It can be seen that apparently normal behaviour predominates in those invididuals with the clinical grading 1, whereas drowsiness is most frequent for those responding adversely to methylpentynol (clinical gradings 2 and 3). Overactivity or aggressive behaviour showed no correlation with the clinical categories. As behaviour stems so manifestly from its affective setting, the behavioural and affective components were grouped together (Table II) to determine whether any associations could be abstracted from the resulting matrix.

It is evident that apparently normal behaviour may occur with euphoria or mild elation and that drowsiness was almost invariably associated with change of mood, particularly depression. Motor overactivity appeared to be linked with the emergence of euphoria or elation. Aggressive behaviour might parade as a modification of attitude, for example, unusually brazen behaviour, lack of tact, or outspokenness, proceeding in one instance to an assault on a nurse (Case 30). It is relevant that this person before receiving the drug had regularly resorted to paranoid mechanisms in his adaptive behaviour. Aggressive reactions were encountered in six subjects (Cases 18, 21, 22, 30, 47, 50). Other behavioural alterations related to appetite, euphoric or elated individuals showing improvement, while those with depression suffered a decline in function.

TABLE II

RELATION OF BEHAVIOUR TO MOOD DURING METHYLPENTYNOL ADMINISTRATION

Behavioural Component	Affected Component			
	Normal	Depressed Irritable	Elated Euphoric	Other Change
Normal	9	1	8	1
Drowsy	3	18	0	3
Overactive	0	0	5	0
Aggressive	0	3	1	2

Affective Changes.—These fell approximately into the triad of no alteration, elation or euphoria, and depression combined with irritability.

Table III sets out the relation of change of mood to the presence or absence of toxic phenomena. It is evident that the absence of mood changes or the development of elation or euphoria is likely to be associated with a grading of no toxicity, while the emergence of depression and irritability is linked with ratings of minimal or maximal toxicity.

The significance of the data was assessed using an arc sine transformation. It was found that the proportion showing affective changes (30 out of 32 subjects) was significantly greater among individuals responding adversely to methylpentynol, than the proportion with mood alterations but without toxic features (12 from 22 subjects), the critical

TABLE III

RELATION OF MOOD TO CLINICAL RESPONSE TO METHYLPENTYNOL

Mood	Clinical Grading		
	1	2	3
Unaltered	10	2	0
Elated, euphoric	9	3	2
Depressed, irritable	2	8	13
Other mood change	1	2	2

ratio being 3·46 ($P < 0·01$). However, euphoria or elation might occur in the absence of other changes attributable to the drug, and of the 14 affected individuals (Cases 3, 6, 12-14, 16, 19, 20, 27, 28, 44, 47, 48, 53) only three were found to have impaired concentration and attention (Cases 3, 44, 53). On the other hand, not only was depression likely to be associated with toxic signs, but its emergence was an almost constant portent of the incipient toxic episode. Irritability came usually to blend with depression, but with negligible tension and without agitation. Perplexity when present was so intermingled with impairment of attention and concentration as to make attempts to place in separate categories artificial. The somatic accompaniments of depression were shown, particularly loss of appetite and motor drive.

Of the six patients who showed aggressive features, in three this canalized from a setting of impaired attention and concentration (Cases 18, 21, 30). All six were manifestly irritable, but only one was depressed (Case 50). Affective qualities, such as ambivalence, inadequate or inappropriate mood, were not seen.

Mood alterations were reversible, usually disappearing within three or four days of withdrawing the drug, but persisting in one patient for three weeks (Case 5).

Talk.—Thought and its consort, conversation, are considered together, abnormalities of either being cited under unified headings relative to production, progression, and content. The two extremes of talk are represented by " uncommunicative " and " garrulous ". Nine patients were described as uncommunicative, this being an unusual attribute of their personality. One was without toxic signs (Case 15), two exhibited minimal toxic changes (Cases 1, 45), while six developed marked toxic signs (Cases 2, 31, 32, 35-37). Garrulity is recorded for nine individuals, four of whom were otherwise unaffected by methylpentynol (Cases 12, 20, 22, 47), three displayed mild toxic phenomena (Cases 18, 30, 41), and two severe toxic changes (Cases 3, 24). Train of thought was facilitated in patients with elation or euphoria, while depressed subjects experienced difficulty in thinking.

Thought content was usually appropriate to the mood change. Thus one depressed individual remarked, " I'm a failure. I'd like to be dead. Will the tablets kill me if I take enough ? " (Case 52). In contrast, a mildly elated patient (Case 6) asserted, " I feel much better . . . in fact, on top of the world. This is the best I've been for years."

Remarks such as these suggest that a patient may judge the efficacy of a drug not by its effect on symptoms, but rather by its capacity to boost mood, and hence modify his attitude towards symptoms.

Digit Span

The mean score and standard deviations for performance on digits forwards and backwards during both a control period and while on the drug was recorded for 49 of the 54 patients. As with the serial sevens test, a control score was determined for approximately half the subjects (24 patients) during the time they were receiving inert capsules, and for the remaining 25 subjects after a lapse of at least a week following withdrawal of methylpentynol. The data are presented in Table IV.

For patients showing no toxic developments, the mean digit score was virtually identical and without significant difference for both control and drug periods. Patients who responded badly to methylpentynol showed a falling off in digit retention. As might be expected, those individuals with maximal toxic developments (clinical grading 3) fared least well, the differences between mean scores for control and drug phases being highly significant for both digits forwards ($t = 5·82$, $P < 0·001$) and digits backwards ($t = 4·76$, $P < 0·001$). Those subjects with minimal toxic developments (clinical grading 2) suffered a smaller decline in performance ascribable

TABLE IV

MEAN DIGIT RETENTION SCORES AND STANDARD DEVIATIONS DURING ADMINISTRATION OF INERT CAPSULES AND METHYLPENTYNOL

Clinical Grading	N	Digits Forward		Digits Backward	
		Control (Inert Capsule)	Drug (Methylpentynol)	Control (Inert Capsule)	Drug (Methylpentynol)
1	22	6·54 ± 0·97	6·27 ± 0·88	4·45 ± 0·82	4·45 ± 0·82
2	13	6·00 ± 0·88	5·46 ± 1·01	4·53 ± 0·88	3·77 ± 0·69
3	14	6·78 ± 1·12	5·21 ± 2·22	5·07 ± 0·72	4·07 ± 1·22

to the drug; for digits forwards $t = 2{\cdot}01$, $P < 0{\cdot}05$ and for digits backwards $t = 2{\cdot}97$, $P < 0{\cdot}01$.

Retrospective Memory

By retrospective memory is meant recollection for that period during which methylpentynol was administered. A designation of moderate impairment of retrospective memory applied when an individual was discovered to have partial amnesia for events during the prescribed interval, and severe impairment of retrospective memory when he was able to give at most a meagre account of events during this time. These ratings were allotted after an interview with the patient at least two weeks after withdrawal of the drug. Details are included in Table V.

TABLE V

DISTURBANCE OF RETROSPECTIVE MEMORY AFTER METHYLPENTYNOL

Retrospective Memory	Clinical Grading		
	1	2	3
Unaffected	21	11	3
Moderate impairment	1	2	9
Severe impairment	0	2	5

The significance of the data was assessed with an arc sine transformation. A significant difference was found between the proportion with memory impairment in the groups evincing no susceptibility to methylpentynol (one subject out of 22) as compared with the proportion with memory impairment and responding adversely to the drug (18 from 32 patients), the critical ratio being 4·69 ($P < 0{\cdot}001$). The inference that memory impairment is much more likely in patients who developed toxic manifestations is thus amply substantiated.

These findings are of interest, inasmuch as impai ment of retrospective memory developed in the absence of disorientation and can only be associated with the impairment of attention and concentration in those individuals responding adversely to the drug; even so, no defect for registration of present events had been noted. No relation was apparent between increasing age and liability to memory impairment, for of the 19 affected individuals only four were over the age of 40 years (Cases 10, 24, 30, 44).

Illusions and Hallucinations

Four instances were encountered, one in a patient with a minimal toxic rating (Case 30) and the other three in subjects with a maximal rating (Cases 3, 5, 52).

The first (Case 3) was that of a man who observed a face on the ceiling, allegedly that of his mother, and heard the muttering of voices. The disturbances occurred on the fourth night of receiving methylpentynol. The patient was an immature person and very attached to his mother. Another patient (Case 5) on the fifth night of the drug insisted she had seen a woman, probably her mother, standing over her bed. The illusion or hallucination occurred only once and the patient realized that it was an unreal phenomenon. This subject was also abnormally dependent on her mother. In the third instance (Case 30) the patient during the third evening of receiving methylpentynol misinterpreted a shadow for a dog and then complained of itching of the skin. These abnormalities recurred each night until the drug was withdrawn. The final patient (Case 52) insisted during the last evening on the drug that his room was full of animals.

In summary, the disturbances, predominantly visual but also aural and perhaps tactile, occurred during the evening. They were fleeting in nature, were recognized as insubstantial and did not provoke an unpleasant affective response. They embodied material occurring normally in the patient's lives, and for at least two of them this was of specific emotional importance.

Body Image

Many morbid states are lent piquancy by alterations in body image, the changes ranging from enhancement to diminution or distortion. In spite of the straightforward categories of Bonnier (1905), descriptive overlap occurred.

Hyperschematia.—One instance was encountered although it could readily be incorporated under paraschematia. The patient (Case 8) complained of a feeling of enlargement of his head and the upper trunk. " My head and face seem swollen, even down to the waist. My hands and arms feel small."

Other individuals complained of " heaviness of the legs " but in all cases the experience seemed unimportant, meriting only incidental allusion.

Hyposchematia.—Some individuals noted " a feeling of lightness of the body or limbs ", but as above, the experiences never brooked large in the symptomatology.

Paraschematia.—Two examples were encountered (Cases 4, 52). One patient remarked " I seem to be two different people. When I brush my hair I feel I do it for someone else." The other related, " I don't seem myself. I don't recognize myself in my name. Nothing belongs to me. It's as if I was outside myself." The experiences of these two patients are reminiscent of what Lhermitte (1939) termed " bipartition of the postural schema and akin to the phenomenon of depersonalization".

Depersonalization and Derealization.—Four examples of depersonalization were recorded (Cases 5, 21, 24, 45). Thus (Case 24): " Everything is altered. My face feels numb and there is no feeling in my teeth. There is no life in my fingers. I just feel cold and dead." There were two instances of derealization (Cases 7, 35). The first (Case 7) remarked: " I feel as if I was miles away. It's a strange impression. The whole world seems distant." Three patients exhibited a mixture of depersonalization and derealization (Cases 25, 26, 30).

Schilder asserts that depersonalization and derealization are almost constantly accompanied by dizziness. This was true for all the affected individuals, but more specifically of the 12 subjects considered above; all but one (Case 30) showed nystagmus or nystagmoid jerks, and all but three (Cases 8, 30, 45) being ataxic.

Alteration in the appreciation of space may be supposed to be implicit in derealization, particularly in expressions relating to the remoteness or distance of the world (Case 7). Such remarks should be interpreted as symbolic expressions of an altered attitude to the outside world rather than true referents to physical space.

Subjective Time Experience

Whereas patients with body image disturbances could be relied on to voice them spontaneously, this was not true for alterations in time experience, evidence for which was only elicited by questioning. Of the 54 individuals, one patient refused information (Case 18), 33 noted no change, 13 stated time seemed to pass more swiftly, while seven insisted that its passage was slower, an extreme example of which is noted (Case 52): " Nothing is happening at all. Everything's slowed down and stopped." Details are included in Table VI.

The significance of the data was assessed using an arc sine transformation. A significant difference was noted between the proportion of subjects with alteration of time experience in the group responding normally to methylpentynol (20 (Table VI) out of 22 patients) as compared with the proportion evincing alteration of subjective time (18 from 31 subjects) and reacting adversely to the drug, the critical ratio being 4·06 ($P < 0·001$). Patients developing toxic phenomena with methylpentynol are therefore more disposed to distortion of subjective time experience than those individuals who respond normally to the drug.

TABLE VI

SUBJECTIVE TIME EXPERIENCE AND CLINICAL RESPONSE TO METHYLPENTYNOL

Subjective Time Experience	Clinical Grading		
	1	2	3
Unaffected	20	7	6
Faster	2	4	7
Slower	0	3	4

Orientation

No subject developed disorientation for time, person, or place while receiving methylpentynol.

Results of Serial Sevens Test

The mean scores and standard deviations for the serial sevens test are depicted in Table VII.

In deference to experimental rigour, the control scores for half the subjects were obtained during the control period before the five-day course of methylpentynol, and for the other half after a lapse of at least one week after withdrawal of the drug. The results were scored both for the number of mistakes, " error score ", with a maximum of 14 mistakes, and for the time taken in seconds to complete the test, time score. However, six individuals were unable to attempt the test after five days of methylpentynol (Cases 7, 18, 21, 24, 26, 30). Of these, two (Cases 18, 30) were minimally toxic, and the rest displayed maximal toxic features. An arbitrary score was obtained for these six subjects by allotting them the mean score derived from the remaining 48 individuals, plus an increment of thrice the standard deviation of the mean score.

The difference between control and drug mean scores for patients in clinical category 1 is not significant. For patients with minimal toxic changes (clinical grading 2) the difference between control and drug mean error scores is not significant ($t = 1·93$, $P > 0·5$), although the mean time required to complete the test while the drug is being administered is significantly increased ($t = 4·37$,

TABLE VII

MEAN ERROR AND TIME SCORES WITH STANDARD DEVIATIONS FOR SERIAL SEVENS TEST DURING ADMINISTRATION OF INERT CAPSULES AND METHYLPENTYNOL

Clinical Grading	N	Error Score (1-14)		Time Score (sec.)	
		Control (Inert Capsules)	Drug (Methylpentynol)	Control (Inert Capsules)	Drug (Methylpentynol)
1	22	0·59 ± 0·98	0·77 ± 1·20	47·14 ± 14·06	48·05 ± 20·43
2	15	1·29 ± 1·02	2·00 ± 1·41	46·07 ± 11·71	70·22 ± 23·74
3	17	0·59 ± 1·08	3·41 ± 1·54	53·53 ± 14·80	84·65 ± 43·08

$P < 0.001$). For subjects who developed a maximal toxic picture, the difference between control and drug mean error scores is significantly augmented ($t = 3.37$, $P < 0.001$) as is the mean time required for test performance ($t = 2.82$, $P < 0.01$).

These results indicate that in the minimal toxic categories accuracy at the serial sevens test is maintained at the expense of a longer period for completing the test, whereas in the maximal toxic categories inaccuracy at the test increases significantly in spite of the greater period devoted to test performance.

Insight

Insight was not impaired while individuals were receiving the drug, but those patients with impaired retrospective memory later experienced difficulty in recalling events and hence assumed logically correct albeit factually incorrect attitudes to the incident.

Withdrawal Effects

Three subjects (Cases 4, 32, 34) seemed worse after the drug was withdrawn, all experiencing nausea and complaining of feeling anxious or being cold and shivering. Vomiting unrelated to food was noted in Case 32. One of the patients (Case 34) became restless and paranoid 48 hours after stopping methylpentynol, misinterpreting shadows for people and objects in the ward as animals. This disturbance subsided within two days.

Electro-encephalograms

The tracings (Fig. 4) came from a patient with maximal toxic features (Case 34). The anomalies consist of 22 to 26 cycles-per-second activity of increased voltage over the frontal and central regions of the brain. These abnormalities were found regularly in subjects graded as maximally toxic, some also showing slowing of the dominant post-central frequency. Minor electro-encephalographic alterations were noted in patients designated as minimally toxic, but not for individuals allocated to clinical grading 1. Three patients with marked behavioural changes, in the absence of abnormal signs following administration of methylpentynol, were rated as clinically toxic on account of electro-encephalographic anomalies (Cases 18, 30, 47).

Other Effects of Methylpentynol

One instance of a generalized urticarial response to methylpentynol was seen (Case 38). This occurred on the third day of drug administration in a patient with a history of asthma, hay fever, and urticaria.

Urine

The urine of patients developing toxic signs

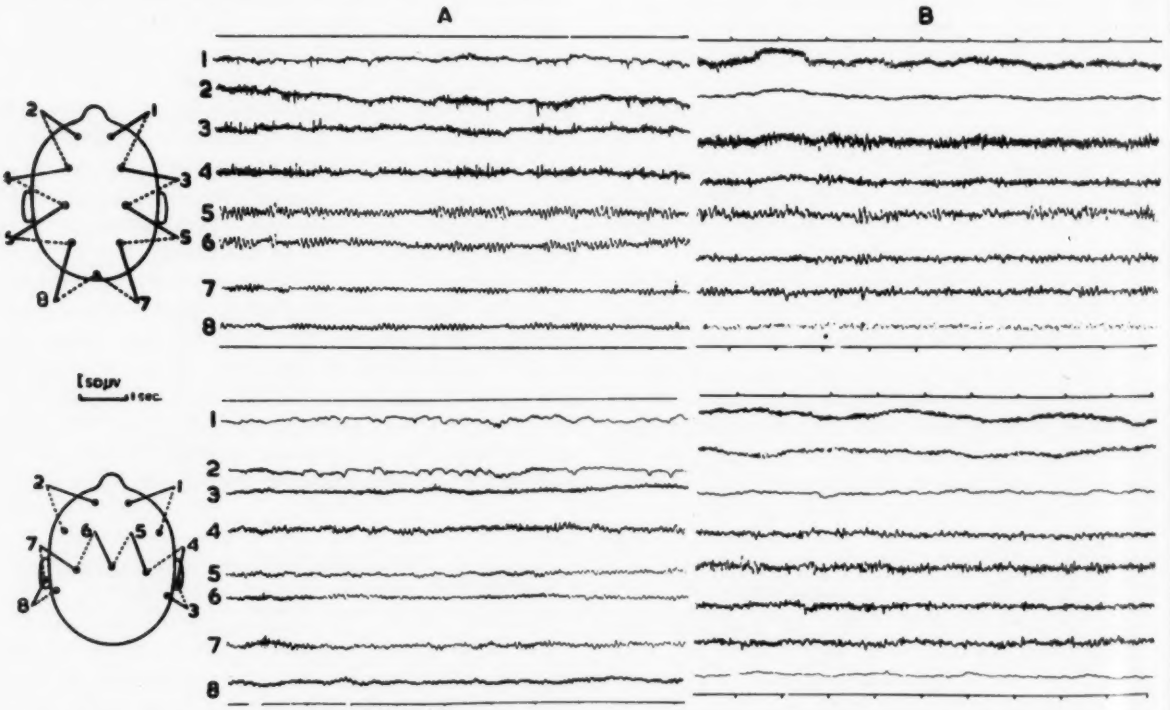

FIG. 4.—Control (*A*) and abnormal (*B*) electro-encephalograms from a subject with methylpentynol intoxication. Upper tracing, high sagittal electrodes; lower tracing, transverse central electrodes. Abnormal records reveal fast activity in the frontal and central areas.

frequently contained a substance that reduced Benedict's solution, appearing first about the third day of the course of methylpentynol. Urinary frequency was also a common complaint.

Placebo Effects

None of the physical signs encountered with methylpentynol were seen when patients were receiving inert capsules, although there were alterations in the mental state, particularly changes of mood. These were noted in nine patients and consisted of the appearance of mild euphoria or depression. The affective changes had subsided in all but three (Cases 6, 21, 36) by the time the active drug was prescribed. No body image disturbances were complained of but six individuals had depersonalization experiences (Cases 15, 18, 32, 41, 45, 47). No other disturbances occurred although alteration of subjective time sense was not enquired for. There was a marked effect on symptomatology, and of the 34 patients in hospital, 10 stated they felt better while receiving inert capsules. The normal subjects noticed no change, as did the majority of the remaining patients, although four insisted there had been aggravation of their state.

There was thus a wide divergence between the effects of placebo and the active drug, so that correlations between the presence of abnormal symptoms and signs and the action of methylpentynol have a significant basis.

Time Incidence of Toxic Phenomena

Thirty-two patients responded adversely to methylpentynol. The distribution for the initial appearance of toxic signs shows peak frequencies on the third and fifth days of drug administration (Fig. 5). Only one instance of toxic response occurred before the third day.

Susceptibility and Dosage

It was conceivable that individuals developing toxic features with methylpentynol might remain free from complications if maintained on a reduced dose. Consequently, six subjects with pronounced susceptibility to methylpentynol were again prescribed the drug. Two were given 1 g. a day. (Cases 21, 34), two received 0·5 g. daily (Cases 24, 36), and two others 0·25 g. daily (Cases 26, 35). None of the six manifested susceptibility although methylpentynol was given for 10 days. Similarly, three patients who were unaffected by the drug were prescribed doses in excess of the original régime (Cases 23, 28, 46). Each received 2 g. a day for five days, succeeded by 5 g. daily for a further two days without the emergence of toxic phenomena.

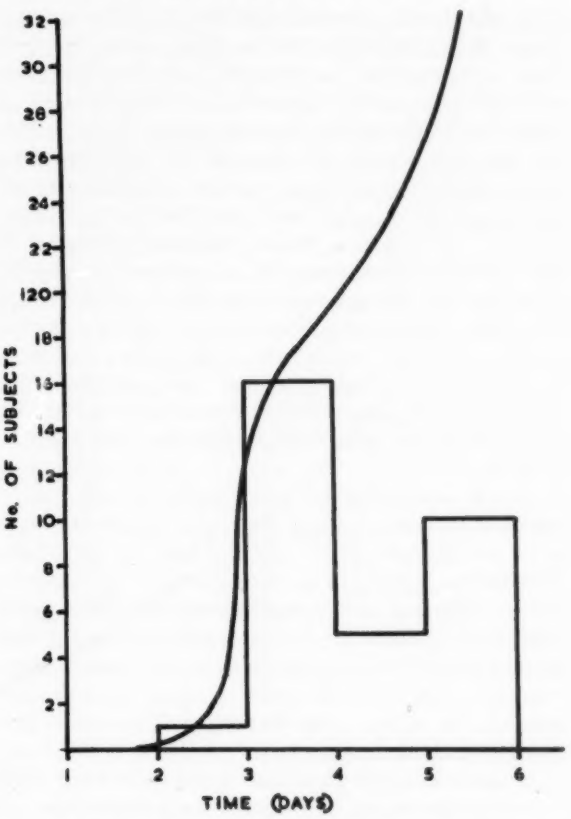

FIG. 5.—Histogram and integrated frequency curve for the initial appearance of toxic signs in 32 subjects responding adversely to methylpentynol.

DISCUSSION

The clinical picture of methylpentynol intoxication emulates that seen following the administration of many central nervous system depressants, there being a particularly telling resemblance to alcohol intoxication. Methylpentynol belongs to the series of higher alcohols, and these tertiary carbinols are known to produce depression of the central nervous system (Jenkins and Hartnung, 1943). As the activity of an alcohol increases with the size of its respective molecule (Gaddum, 1956) it is scarcely surprising that methylpentynol with its branched six-carbon chain should produce side-effects in a proportion of individuals.

Howells (1952) depicts the findings in 40 persons suspected of being under the influence of alcohol, including pupillary dilatation with impaired reaction to light or accommodation, suffused conjunctivae, nystagmus, and ataxia with a positive Romberg sign. Identical phenomena have been elicited in barbiturate poisoning, and Isbell and White (1953) have pointed to the similarity between alcohol and barbiturate intoxications.

In our series, the presence of nystagmus on conjugate lateral deviation of the eyes as early as three days after beginning methylpentynol was a reliable indicator of a portending toxic reaction and confirms Howells' (1956) finding that nystagmus is the earliest eye sign produced by alcohol. Pupillary reflex abnormalities were found in only one-third of our group and consisted of impairment of the reaction to light and to accommodation, although dilatation of the pupils in the absence of any alteration of reflex response to stimuli was commoner still. Other anomalies included suffused conjunctivae, diminished corneal reflexes, diplopia, dysarthria, and fine tremor of the protruded tongue. In a quarter of the individuals, the lower facial masculature suffered a striking loss of tone accompanied by unilateral or bilateral ptosis.

Ataxia when present was of either cerebellar or posterior column variety or a mixture of the two. In consequence, limb muscle tone was usually diminished, although in one instance quoted by Hirst (1955) and in two patients seen by Marley and Chambers (1956) muscle tone was augmented and accompanied by sustained patellar and ankle clonus. Similarly, Isbell (1950) found that chronic barbiturate intoxication might present with ankle clonus and extensor plantar responses.

Paraphasia and nominal dysphasia were also encountered, being presumably an expression of general disturbance of central nervous function. Curran (1944), who believed that he could distinguish features specific to drug intoxications, stipulates that paraphasia is one of the hall marks of bromide deliria. There seems to be no logical grounds for assuming such symptomatological exclusiveness, and Mayer-Gross, Slater, and Roth (1954) allude to its occurrence in delirium tremens. Stengel and Mayer-Gross (1945) refer to paraphasic disturbances during recovery from hypoglycaemia. They noted, in deference to Paterson's criticism of a quantitative one-dimensional idea of consciousness (Paterson, 1944), that there were at least four levels of consciousness during hypoglycaemic arousal, paraphasia being associated with the least clouding of consciousness.

One of the other diverting facets of the action of methylpentynol was its ability to produce differential mood alterations, this effect being seen both in individuals manifesting toxic features and in those who did not. The spectrum of mood ranged from elation to depression, the development of a blend of depression and irritability being a constant harbinger of the emergence of neurological abnormalities. Ideational content remained congruous with the prevailing mood, to the extent even of suicidal ideas being expressed during a depressed period.

Euphoria and elation were usually noted in patients without toxic signs. Wikler (1952a) suggested that in such circumstances euphoria or dysphoria were related each to the other in that both crystallized out when the sensorium was impaired. We would concur with this finding for our series when depressive features were predominant, but it was not the case when mood was heightened.

The eventual pattern produced by the drug seemed independent of the original pattern of mood for the subject, but all affective changes were rapidly reversible, usually abating within a few days of withdrawing the substance. Alteration in motor activity and appetite appeared subordinate to the particular mood deviation. Mood changes in drug intoxication seem therefore of a non-specific character and have been so categorized by Thorner (1935), Cleghorn (1952), and Wikler (1952b). In spite of these precedents, there is little allusion to the potential adverse effect of the tranquillizing agents on mood. However, Dickel and Dixon (1957) have noted that individuals who should benefit from the drugs instead develop untoward reactions. Anxious people become depressed enough to commit suicide; easy-going people become hypomanic or manic. It is of interest then that Curran (1944) witnessed apparent hypomanic episodes in some cases of barbiturate poisoning.

Disorientation has also been described as a toxic response to methylpentynol (Hollander, 1954). Levin (1951) formulated the entity of " partial delirium " which depended on the fact that orientation for time, being an abstract concept, was more vulnerable and consequently more likely to be upset than either orientation for place or for person. None of our patients exhibited disturbance of this modality, although attention, concentration, and abstract thought were impaired. Trotter (1954) found that speed of reaction, concentration, and coordination were either unimpaired or enhanced after 0·5 g. of methylpentynol, although Macdonald (1955), using 0·25 g. noted an 8% deterioration on a numerical test. Kornetsky (1951) reported a decline in digit retention associated with the long-term administration of barbiturates, while earlier still Hoch (1906) noted reduction of digit span with drug intoxications.

Visual illusions or possibly hallucinations occurred infrequently, their content little more than projected material of current psychopathological import to the patient. For this reason they might be regarded as epiphenomena, although the personal nature of such material is well-recognized. Noyes (1948a) remarks that not only are illusions likely to be determined by the prevailing trend of the patient's preoccupations, but that the mental material which

is externalized in the form of hallucinations is of a most intimate, subjective, and personal nature (Noyes, 1948b).

Recollection and recall are said usually to be good after confusional illnesses (Wolff and Curran, 1935) although mild to severe amnesia was the rule for patients who had developed pronounced toxic features. This might be considered surprising as orientation had remained intact. Bleuler (1951) suggested that disturbances of memory are the residue of diffuse interference with cerebral function, and to this the amnesia could be most sagaciously ascribed. Age is considered an important determinant in the development of amnesic syndromes, being the lot of the elderly rather than the young. We found no apparent correlation with age, presumably as the age range was circumscribed.

Disorders of body image were also apparent, the commonest being dizziness and sensations of lightness or heaviness either of the whole or of parts of the body. Feelings of unreality amounting to depersonalization or derealization were spontaneously mentioned. Schilder (1935a) has commented on the frequency of dizziness as an accompaniment to these experiential disorders. Certainly the majority of our patients so affected displayed abnormalities such as ataxia or nystagmus. Although one subject became depersonalized while receiving inert capsules, no patient admitted to a prior experience of a reminiscent quality, and there was no evidence in our series that reactions of this type constitute a preformed functional response as suggested by Mayer-Gross (1935).

A more specific disturbance of body image attributed to methylpentynol involved the head and upper part of the trunk, and Schilder (1935b) refers to the well-known experience of the head seeming larger after alcoholic intoxication. Such features are not confined to an aftermath of alcohol, and Critchley (1950) quotes Chapman as experiencing like phenomena while suffering from hunger and malaria (Chapman, 1949). The complaint of two other patients were akin to those that Lhermitte (1939) has dealt with under bipartition of the postural schema. All types of disturbance were classifiable into Bonnier's categories of hyper-, hypo-, and paraschematia, the best examples of which are usually seen in drug intoxications (Critchley, 1950).

Anomalies of subjective time experience occurred but could only be elicited by questioning. Time was said to pass more rapidly, or, less commonly, more slowly, the rate of passage of subjective time being apparently independent of the prevailing affective state although alteration of subjective time experience was found to be linked with an adverse response to methylpentynol. Hughlings Jackson (1932) suggested that this particular " prolongation " of time was the outcome of shallow dissolution of the highest centres and could be interpreted as a more rapid (or slower) succession of a time-constant peculiar to each individual. That anomalies of time experience should occur at all is hardly surprising for, as Lewis (1932) remarks, " It [abnormal time experience] is a primary alteration of consciousness and may be found almost as often as it is looked for in mental disorder."

Electro - encephalographic abnormalities were found at the height of intoxication and occasionally occurred with behavioural anomalies although in the absence of other toxic signs. The disturbance consisted of 22 to 26 cycles-per-second activity of increased voltage over the frontal and central regions of the brain. Although Tükel and Tükel (1952), who examined children sedated with 0·25 to 0·75 g. of the substance, remarked that the records exhibited no features attributable to its action, Henry (1953) and Williams (1954) have drawn attention to minor alterations in the electro-encephalogram after the drug. This is theoretically to be anticipated, and the presence of 20 to 30 cycles-per-second wave activity in the frontal, and less often in the parietal, region has been noticed after administration of barbiturates (Brazier and Finesinger, 1945; Lennox, 1946). Cohn and Katzenelbogen (1942) suggest that this is not a specific barbiturate effect but may occur with cyclopropane anaesthesia and during the early stages of deep sleep.

Elaborate withdrawal symptoms after discontinuing the five-day régime of methylpentynol were evident in one instance. As noted by Isbell, Altschul, Kornetsky, Eisenman, Flanary, and Fraser (1950) for barbiturate addicts, anxiety, tremor, nausea, and insomnia appeared within 24 hours of stopping the drug, being succeeded by illusions and hallucinations after a lapse of three days. A small number of individuals developed nausea and even vomiting after ceasing methylpentynol but without the emergence of other symptomatology. The drug can therefore be fairly described as mildly habituating.

No skin reactions to methylpentynol as portrayed by DeLamater (1952) were encountered, although one patient with a history of allergic phenomena developed urticaria within three days of starting to take the drug.

The urine of patients developing toxic signs frequently contained a substance that reduced Benedict's solution. This was presumably due to the excretion in the urine of a breakdown product of methylpentynol conjugated with glycuronic acid, as has been shown to occur by Perlman, Sutter, and Johnson (1953). Complaints of urinary frequency were common when subjects were receiving the drug, and although no objective measurements of augmented

fluid excretion were obtained, the diuretic action of alcohol is well authenticated (Eggleton, 1942).

As geometric increments or decrements of dose are related to arithmetic increase or decrease of drug response, it was presumed that subjects becoming toxic with 2 g. daily of methylpentynol might remain free from adverse effects if the dose of the substance was reduced in geometric fashion. This assumption was found to hold good. Similarly, some patients manifested no ill effects from doses of methylpentynol well above the maximum recommended for sedation. Even so, it must be contended that for some individuals, methylpentynol accumulates in the body and that a dose of 2 g. a day is not only excessive but well above the level that should be employed for long-term sedation.

SUMMARY

Fifty-four individuals were prescribed 0·5 g. q.d.s. of methylpentynol for five days, preceded by a similar period on inert capsules.

Toxic effects appearing between the third and fifth day of the drug régime were seen in 32 subjects, all of whom recovered completely within four days of withdrawing methylpentynol.

The toxic phenomena included pupillary abnormalities, nystagmus, suffusion of the conjunctivae, ptosis, loss of facial muscle tone, dysarthria, tremor of the protruded tongue, and cerebellar ataxy in the limbs or admixtures of this with posterior column ataxia. Muscular tone was diminished as were the tendon reflexes. Electro-encephalographic abnormalities were encountered.

Mood change, particularly depression with irritability, dominated the accompanying mental state. Orientation was preserved even in a setting of impaired attention and concentration. Nominal dysphasia, paraphasia, and distortion of subjective time experience and body image were noted. Illusions or possibly hallucinations occurred, as did impairment of retrospective memory for the toxic episode. Prominent withdrawal features were seen in one instance.

It is contended that the drug accumulates in the body, and that a dose level of 2 g. a day is too high for long-term sedation.

We take pleasure in thanking Dr. Denis Leigh for his kind permission to publish, Dr. A. E. Maxwell for invaluable statistical advice, and British Schering Ltd. for a generous supply of methylpentynol and inert capsules. We are indebted also to Mr. D. A. Green for preparation of the figures.

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AN INVESTIGATION OF THE ROSENOW ANTIBODY ANTIGEN SKIN REACTION IN SCHIZOPHRENIA

BY

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In view of Bering's (1951) confirmatory work on the Rosenow antibody-antigen skin reaction in idiopathic epilepsy, it was decided to carry out similar tests at Shenley Hospital with schizophrenic and epileptic groups of patients, in order to see if further confirmation could be obtained, particularly in schizophrenia.

Rosenow's findings have been reported extensively (1947, 1948a, 1948b), but so far the only confirmatory work is that of Bering. In essence, Rosenow believes that a streptococcus of the alpha viridans type plays a significant part in the aetiology of a wide variety of diseases, among which are included epilepsy, schizophrenia, and arthritis. He claims to have demonstrated, using a variety of tests, that patients suffering from any of these groups of diseases harbour alpha-haemolytic streptococci of different types in the naso-pharynx, which are in some ways specific for patients suffering from that particular disorder or group of disorders. One of the ways in which this can be most readily demonstrated is by a cutaneous reaction to an intradermal injection of specific streptococcal antibody, or antigen (Rosenow, 1948c). For practical purposes he finds that a specially prepared antibody, designated "thermal antibody", and prepared according to a carefully described technique, is equivalent to natural antibody prepared by the immunization of animals. According to Rosenow (1948b), this substance, when injected into the skin of patients suffering from diseases similar to those in which the streptococci, from which antibodies have been prepared, were first isolated, produces a higher proportion of large erythematous reactions than when the same substance is injected into well persons, or persons suffering from other disorders. The differences in response so produced appear convincing even without careful statistical analysis. Furthermore, Bering (1951) demonstrated statistically in his own experiments that these findings, in epilepsy at least, are significant beyond all reasonable doubt.

Methods

Material for use in testing was obtained direct from Dr. Rosenow, and had been prepared by him according to the techniques described and found to give significant results in patients in the U.S.A. These were sent to us in rubber-capped bottles, labelled *A*, *B*, *C*, and *F*. Substance *A* consisted of thermal antibody prepared from cultures of alpha-haemolytic streptococci, isolated from the naso-pharynx of patients suffering from schizophrenia, *B* from patients with epilepsy, *C* from patients with arthritis, and *F* from people who were clinically well at the time. Two sets of these were sent over by air, and one set (selected by tossing a penny) was immediately returned to Dr. Rosenow for testing on American patients to confirm that no change had occurred as a result of transit, and he was in fact able to confirm that this was so.

Case Material

Patients known personally to only one of us (W. P. G.) were selected according to the diagnosis. Later, after all the tests had been performed, this was confirmed or rectified by both of us, on scrutinizing the case records and interviewing patients where any doubt existed. Atypical features were also noted. All patients were submitted to testing by three observers, under standard conditions of lighting. There was some variation in room temperature, because most patients were tested on cold days, and the others when the weather was warmer. According to Dr. Rosenow (personal communication) the temperature of the wards had no significant influence on cutaneous reactions in his series.

Patients.—These were male patients, mainly long-stay, living for the most part in close association with one another, although suffering from different disorders. Sixty-seven patients were tested in all, and among these were 40 schizophrenics, 16 epileptics, and 11 patients suffering neither from epilepsy nor schizophrenia, to act as controls. Of this last group there were five with general paralysis of the insane (non-convulsive), two manic-depressives, and four with personality disorders.

Technique

The technique was applied as described by Rosenow (1948b). The volar aspect of the forearm was used for all injections, and cutaneous tests were made by injecting

intradermally, as superficially as possible, 0·03 ml. of each solution. Separate clean and sterile syringes were used in each series of tests. Furthermore, each syringe was clearly labelled *A*, *B*, *C*, or *F*, and was used only for the appropriate test substance. Tests were also carried out to show the influence of the quantity injected, but no significant changes were observed whether 0·03 plus or minus 0·01 of a millilitre was injected. It was usually possible not to exceed this error. No attempt was made to discover what drugs the patients were taking at the time, since Rosenow (1955) claims that in epileptics and in schizophrenics drugs such as epanutin, phenobarbitone, or chlorpromazine have little or no effect on the size of cutaneous reactions. Frenquel, which was not used in any case in this series, does apparently significantly increase reactions. No attempt was made to establish in the epileptic patients the relationship in time between testing and occurrence of seizures, although Bering (1951) and Rosenow (1948b) have claimed that the size of the reaction does vary in this respect.

Results and Conclusions

Schizophrenic Group.—Forty schizophrenic patients were tested, their ages varying from 21 to 55. No influence was noted in relationship to age or duration of illness nor to the type of illness.

	A	*B*	*C*	*F*
Average responses (sq. cm.)	4	3·6	2·5	2
Range of responses (sq. cm.)	0–15	0–24	0–17	0–10

All responses were measured by square centimetres of erythema, which was usually maximal about five minutes after injection, and agreed upon by all three observers, using a standard series of circles on a transparent *x*-ray film, supplied by Dr. Rosenow.

Positive reactions, as defined by Rosenow (1948b), are those greater than 5 sq. cm. If this value is taken as critical, we found the above in schizophrenic patients.

It was also noted that of the 16 patients reacting positively to *A*, eight also reacted positively to *B*, and one to *C*. Fourteen out of 40 schizophrenic patients showed some degree of reaction to all injections, but in 10 of these the reactions to *A* and *B* were greater than *C* and *F*. When the results of the schizophrenic group were examined according to the positive or negative reactions, no significant difference was found in the two groups, each containing an equal proportion of borderline or doubtful cases. Ten patients were positive both to *A* and *B* and not to *C* or *F*. Eleven patients showed greater reactions to *B* than to *A*, and two of these were positive to *B* alone, and one to *B* and *F* alone. Only three patients out of the 40 showed hardly any reaction to any of the antibodies, that is, less than 2 sq. cm. Two of these were the most normal clinically, in behaviour and appearance. Three cases reacting to *A* only and showing no response to the other three antibodies were all atypical with cycloid features. Of the four schizophrenic patients positive to *B* and not to *A*, one had had a leucotomy, but the other three presented no unusual features.

Epileptic Group (Aged 22-59).—Sixteen patients were tested. These were divided into the following groups, namely, idiopathic, eight; traumatic, three, and aetiology doubtful, five.

	A	*B*	*C*	*F*
Average responses of the whole group (sq. cm.)	3·5	2·6	3·3	1·0
Range of responses (sq. cm.)	0–11	0–12	0–20	0–5
Positive reactions: idiopathic epilepsy	2/8	3/8	0/8	0/8

Two of the three positive to *B* were also positive to *A*. One with a greater response to *A* was an epileptic of late onset. The average size of responses of idiopathic cases was: *A*, 3·5 sq. cm.; *B*, 2·75 sq. cm.; *C*, 2 sq. cm.; *F*, 0·375 sq. cm.

Of the three traumatic cases, one was positive to *B*, one positive to *A*, but none to *C*, and one did not react at all to any of the substances injected. Five out of the 16 epileptics tested did not react to any of the test substances, and these were found in all three groups, although housed in the same wards, and living in close contact with other patients tested.

	A	*B*	*C*	*F*
Positive reactions	16/40 } 24/40	15/40 } 20/40	4/40 } 10/40	5/40 } 11/40
Doubtful reactions bordering on 5 sq. cm.	8/40 } 24/40	5/40 } 25/40	6/40 } 36/40	6/40 } 35/40
Negative reactions, that is, less than 5 sq. cm.	16/40	20/40	30/40	29/40

Non-epileptic, Non-schizophrenic Group.—This miscellaneous group consisted of 11 patients as described above, ages ranging from 35 to 65. The average reactions of this group were:—

	A	*B*	*C*	*F*
Average responses (sq. cm.)	4	3	2	1·6
Range of responses (sq. cm.)	0–11	0–12	0–5	0–5
Positive cases	4/11	3/11	2/11	2/11

Of the five cases of G.P.I., three were positive to *A* and *B*, and one other reacted more to *A* and *B* than

to *C* and *F*, although not reaching the critical value of 5 sq. cm. Of those four suffering from personality disorders, one was positive to *A* and the others were negative. The two manic depressive patients were both positive to *C* only. One of these had sciatica, and the other was osteo-arthritic.

From these results it can be seen that the tests do not seem clearly to distinguish between any of the three groups of patients tested.

Positive to A
Schizophrenics ..... 16 out of 40 (40%)
Epileptics (total) ..... 4 out of 16 (25%)
Idiopathic ..... 2 out of 8 (25%)
Controls ..... 4 out of 11 (36%)

Positive to B
Schizophrenics ..... 15 out of 40 (36%)
Epileptics (total) ..... 5 out of 16 (30%)
Idiopathic ..... 3 out of 8 (37·5%)
Controls ..... 3 out of 11 (27%)

Positive to C
Schizophrenics ..... 4 out of 40 (10%)
Epileptics (total) ..... 1 out of 16 (6%)
Idiopathic ..... None
Controls ..... 2 out of 11 (18%)

Positive to F
Schizophrenics ..... 5 out of 40 (12%)
Epileptics ..... None
Controls ..... 2 out of 11 (18%)

While the total numbers are small, the results have been expressed as percentages to enable easy comparison with Rosenow's (1948b) figures, which are also expressed in the same way. In the case of schizophrenics at least the error produced by so doing remains reasonably small.

Average Responses of Three Groups Compared.—Responses to *A* and *B* are consistently and considerably greater than to *C* and *F* in all groups, and are as follows:—

	A	*B*	*C*	*F*
Schizophrenics	4	3·6	2·5	2
Epileptics (idiopathic)	3·5	2·75	2	0·375
Controls	4	3	2	1·6

If we examine the above results we see that a slightly greater proportion of schizophrenics react to *A* than to *B*, and a slightly greater proportion of epileptics react to *B* than to *A*. However, both groups show a significantly greater proportion of reactors to *A* and *B* than they do to *C* and *F*. Considered in terms of the actual size of response rather than the number of persons reacting in any group, again we find that both schizophrenics and epileptics show a greater average size of response to *A* and *B* than they do to *C* and *F*. However, this tendency is also present to an equivalent degree in the control groups. Also, the control group shows a greater number of positive reactors to *A* and *B* than to *C* and *F*. It is our opinion, therefore, that these results are in no way specific for the groups tested. Looking at Rosenow's (1948b) findings, we see that he claims the following average responses:—

89 schizophrenics
To *A* ..... 7·49
To *B* ..... 4·53
To *C* ..... 0·89

41 idiopathic epileptics selected without regard to severity or contact with schizophrenic patients
To *A* ..... 5·15
To *B* ..... 9·63
To *C* ..... 2·45

24 cases of G.P.I. without fits
To *A* ..... 1·75
To *B* ..... 1·9
To *C* ..... 0·89

Our figures show no such trend as those of Rosenow, in whose results the average response of schizophrenics is far greater to the antibody derived from schizophrenic patients, the average response of epileptics is far greater to the antibody derived from epileptics, and the average response of cases of G.P.I. is negative to all the antibodies used. It will be noted, however, that many of Rosenow's schizophrenics react quite strongly to *B* as well as to *A* and many of his epileptics react to *A* as well as to *B*.

Expressed as percentages of positive results in these groups, Rosenow's (1948b) figures differ decidedly from ours.

Positive to A
Schizophrenics 76%
Idiopathic epileptics 59%
G.P.I. 4%

Positive to B
Schizophrenics 58%
Idiopathic epileptics 96%
G.P.I. 0%

Positive to C
Schizophrenics 20%
Idiopathic epileptics 21%
G.P.I. 4%

Here again, there is a large difference, in that only 40% of our schizophrenics were positive to *A*, 37·5% of our epileptics were positive to *B*, and 36 and 27% of our miscellaneous group, including patients with G.P.I., were positive to *A* and *B* respectively. Although the numbers of cases we have tested is small in comparison with Rosenow's series (1948b), in the schizophrenic group at least the discrepancy between the proportion of positive reactors and average responses and those found by Rosenow (1948b) fails to support his findings. In our opinion, these substances are not specific in any way for the groups of chronic patients tested. An explanation is still required, however, as to why it is that patients of all groups react more to *A* and *B* antibodies than they do to *C* and *F*. This is also true of Rosenow's findings.

These results agree in principle with those obtained by one of us (H. H. F.) in former studies (1953-54) which were carried out entirely blind. Dr. Rosenow had sent over four antibodies labelled *A*, *B*, *C*, and *F*, together with a control solution containing no antibodies. Tests were carried out in September, 1953, using eight normal controls at first from the laboratory and nursing staff. Amongst others some very large reactions were obtained, but these were due to the syringes not having been allowed to cool down sufficiently after sterilization. When this error was excluded only small reactions occurred.

Then 19 male schizophrenics and 21 male controls were selected from their case notes, the individual patients being unknown to the experimenter when they came up for injection. Only after the results had been recorded by three observers were the identity and diagnoses of the patients revealed. Then the findings obtained in the individual patients were tabulated according to the symbol of the substances to which they reacted, and these results were sent to Dr. J. N. Cumings of the National Hospital, Queen's Square, London, who had kindly agreed to act as " intermediary ". After this, Dr. Rosenow made known the nature of the solutions to Dr. Cumings, who then gave us the relevant information, that is, as to whether *A*, *B*, *C*, and *F* were derived from schizophrenic, epileptic, arthritic, or well person groups. The results were entirely contradictory. Dr. Rosenow was informed of this, and at his request the solutions were returned to him for re-testing. He reported that some of the antibodies had deteriorated. It was then decided to repeat the test the following summer (1954) using a fresh set of thermal antibodies provided by Dr. Rosenow, Dr. Cumings again acting as intermediary. Experimental conditions were altered in two respects: (1) The patients were selected by someone not concerned with the testing. (2) For purposes of measurement, circles on *x*-ray films kindly sent by Dr. Rosenow were used.

The following positive reactions were obtained in 60 male patients:—

	A	*B*	*C*	*F*
Schizophrenics	17/33 (51%)	17/33 (51%)	3/33 (9%)	6/33 (18%)
Epileptics	4/6	4/6	1/6	4/6
Controls	2/21	3/21	0/21	2/21

These results differ only in a few minor respects from those described in the main part of this paper, namely, that (1) average reactions were on the whole larger, possibly due to the tests being carried out in the summer. (2) There was a somewhat greater proportion of positive reactors in the typical schizophrenic group (13 out of 17). On the other hand, 11 out of these same 17 people reacted positively to the epileptic antibody.

A group of eight old organic controls with dry skins gave negative reactions. Another group of four young mental defectives gave average responses to all solutions of the same order as those obtained in typical schizophrenics.

Summary and Conclusions

In this work an attempt has been made to confirm the specificity of Rosenow's antibody-antigen skin reactions, especially in schizophrenia. In three series of tests carried out since 1953 (two of them "blind"), we were unable to confirm that this reaction was specific or of diagnostic value in the group of patients tested, *i.e.*, Rosenow antibodies failed to distinguish between schizophrenic and epileptic groups of patients. In the first series, the results were entirely contradictory, and Dr. Rosenow, after re-testing using the same materials, found that some deterioration of the antibodies had taken place.

In the next two series, 127 patients were tested (73 schizophrenics, 22 idiopathic and traumatic epileptics, and 32 controls suffering from neither of these disorders). The following results were obtained:—

Positive to:	*A*	*B*	*C*	*F*
Schizophrenics	33/73 (45%)	32/73 (45%)	7/73 (10%)	11/73 (15%)
Idiopathic epileptics	6/14 (43%)	7/14 (50%)	1/14 (7%)	4/14 (28%)
Controls	6/32 (18%)	6/32 (18%)	2/32 (6%)	4/32 (12%)

From our findings we may conclude that (1) thermal antibodies prepared by Dr. Rosenow from streptococci, isolated and cultured from groups of patients with schizophrenia (*A*) and epilepsy (*B*), produce larger reactions when injected into patients suffering from schizophrenia and epilepsy than do antibodies derived from streptococci, isolated and cultured from patients suffering from arthritis (*C*), or well persons (*F*).

Likewise, these same substances *A* and *B* produce a greater proportion of positive responses in patients suffering from epilepsy and schizophrenia than do substances *C* and *F*.

In a control series of patients suffering from neither epilepsy nor schizophrenia the average responses are slightly greater to *A* and *B* than to *C* and *F*. The proportion of positive responses is also greater, but less than half of that found in the schizophrenic group.

An interesting impression requiring further investigation is that people who are clinically well and patients in any of the groups tested who appear to

behave relatively normally tend to react negatively to all four substances. However, it was not the purpose of this paper to establish this point.

We should like to thank all those who have helped us with this work, particularly Mr. Warne and Mr. Hadley in the laboratory, members of the nursing staff at Shenley Hospital, and Miss E. Fellowes for her secretarial help. We should also like to thank Dr. E. C. Rosenow for his helpful cooperation and encouragement in carrying out this study, and Dr. S. T. Hayward, of Shenley Hospital, for permission to carry out the work.

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THE FEBRUARY (1958) ISSUE

The February (1958) issue contains the following papers:—

The Relative Merits of Encephalography and Ventriculography for the Investigation of Intracranial Tumours. Gösta Norlén and Ingmar Wickbom.

Ischaemic and Post-Ischaemic Numbness and Paraesthesiae. P. W. Nathan.

The Surgical Prognostic Significance of the Electroencephalographic Prediction of Ammon's Horn Sclerosis in Epileptics. W. A. Kennedy and Denis Hill.

A Report of Two Cases of the Juvenile Form of Amaurotoc Familial Idiocy (Cerebromacular Degeneration). Michael Jefferson and M. L. Rutter.

Spinal Angioma with Symptoms in Pregnancy. M. J. D. Newman.

Pulsating Exophthalmos in von Recklinghausen's Disease. Charles Langmaid and Alex Daws.

Optic Atrophy and Nerve Deafness in Diabetes Mellitus. D. A. Shaw and L. J. P. Duncan.

Sodium Amytal and Extraversion. S. G. Laverty.

A Controlled Trial of Methyl Phenidate (Ritalin) in the Treatment of Depressive States. A. A. Robin and S. Wiseberg.

Epinephrine Metabolites and Pigmentation in the Central Nervous System in a case of Phenylpyruvic Oligophrenia. J. H. Fellman.

Proceedings of the Society of British Neurological Surgeons: 56th Meeting.

Book Reviews.

A number of copies are still available and may be obtained from the Publishing Manager, British Medical Association, Tavistock Square, W.C.1, price 17*s.* 6*d.*

J. Neurol. Neurosurg. Psychiat., 1958, **21**, 146.

MULTILOCULAR CYSTIC ENCEPHALOPATHY OF INFANTS

BY

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Some of the many variants of infantile cerebral cavitation (cystencephaly) fall into morphologically classifiable groups. One of these is symmetrical multilocular cystic encephalopathy of infants, examples of which have been reported under such names as " multiple cystic softening of the brain in the newborn ", " progressive degenerative encephalopathy ", " encephaloclastic porencephaly ", " polyporencephaly ", " multilocular encephalomalacia ", and so on.

Such brains are usually smaller than normal and show multiple cavities in the greater part of both cerebral hemispheres. The lesions are situated mainly in the outer part of the white matter and the inner layers of the cortex, although the entire substance of the brain may be involved in some areas. The cavities are separated from each other by gliosed tissue of varying thickness and many of the cysts are traversed by fine trabeculae. The temporal lobes, below the superior temporal gyri, are often spared. The basal ganglia and all lower formations are also usually intact save for a few microscopical lesions and some secondary degeneration of the cortico-fugal tracts. Histologically, the picture is composite, presenting different stages of complete or incomplete softening and leading up to final resorption of the debris. Many of the smaller cavities are filled with fat-laden phagocytes and the latter are also scattered diffusely in the adjoining solid tissue formed mainly by varying numbers of protoplasmic and fibrous astrocytes. The pleomorphism has been usually interpreted as evidence of progressiveness. It is also compatible, however, with uneven speed of repair and resorption in different areas following upon a single attack of a non-progressive disease.

Since most of the recorded cases were infants dying in early infancy, progressiveness is difficult to establish. The clinical course is usually one of marked neonatal distress followed by failure of development, convulsions, paralysis, and difficulty in feeding. The immediate gravity of the condition leaves little room for the manifestation of any possible progressive deterioration.

No significant vascular lesions have been demonstrated in the majority of the recorded cases. Some workers, however, published a few instances of similar but, except in one case (Von Cseh, 1937), more restricted cerebral changes which were associated with marked arterial lesions of obscure origin. They referred to this arterial condition descriptively as " subendothelial proliferation of connective tissue ". These recorded cases will be mentioned below.

The aetiology of the condition is obscure although some workers, following Schwartz (1924), attributed it to perinatal causes.

Its pathogenesis attracted attention on account of its close morphological similarity to swayback in lambs (Innes and Shearer, 1940; Winkelman and Moore, 1942; Lumsden, 1950) and the bearing that this may have on human demyelinating diseases.

The purpose of this communication is to report another example of this condition following neonatal asphyxia and associated with both arterial and venous lesions.

Case Report

The birth of the patient, an only child of healthy parents, began spontaneously and at term. The first stage of labour lasted 12 hours and the second one hour, during which episiotomy was performed as the child was becoming distressed. The umbilical cord was once round the neck but did not seem to be excessively tight, and the child was in fact slipped through the loop of the cord during the process of delivery. The infant, a male, weighed 3·2 kg., and suffered from asphyxia which was treated by intragastric oxygen, " synkavit ", coramine, and artificial respiration. Breathing was established after one hour and 45 minutes, and six hours later he vomited some blood. The provisional diagnosis was intracranial haemorrhage possibly due to haemorrhagic disease of the newborn. He was kept in oxygen. Within two days he developed a " cerebral cry ", spasticity of the limbs, and head retraction, and was thought to be dying. He recovered sufficiently, however, to be discharged with the mother at 20 days. At home his feeding was difficult; he regurgitated food through the nose and failed to gain weight. At 5 weeks he was admitted to a paediatric hospital.

At this time, and often later, he was drowsy and hypothermic (93·6° F.). The head circumference measured 36·2 cm. and the fontanelles were normal. *Monilia albicans* was grown from a throat swab and the urine contained many yeast-like bodies. The E.S.R. was 41 mm. in one hour. A radiograph of the chest and long bones and the Mantoux reaction (1 : 1,000) were negative. After treatment with penicillin and streptomycin the temperature gradually rose to a normal level in four days. He gained some weight, the E.S.R. fell to 28 mm. in one hour, and he was discharged after 10 days. When seen again in 10 days' time the temperature was down once more to 95° F., and he had gained no weight. He was still drowsy, with a dry skin and oral thrush. The Hb was 67%, E.S.R. 17 mm. in one hour, and the W.B.C. 16,000, with a normal differential count. He continued to be difficult to feed, and cried weakly and hoarsely.

When 3½ months old, he was readmitted to hospital. He was then gravely ill, feeble, grossly dehydrated and cyanosed, with a temperature too low to record. Oral thrush and signs of bronchopneumonia were noted. The abdomen was protuberant, and the liver and spleen palpable 2·5 cm. below the costal margin. The Hb was 63%, the cerebrospinal fluid contained 90 R.B.C.s and 9 W.B.C.s, 40 mg. of protein and 63·5 mg. of sugar per 100 ml. The serum sodium level was 315 mg./100 ml., potassium 22 mg./100 ml., and urea 20 mg./100 ml. He was placed in an oxygen tent and given antibiotics and saline. In spite of treatment his condition soon deteriorated and he died in a few days.

Pathological Findings

The available post-mortem notes mention severe bilateral confluent bronchopneumonia and enlargement of the cervical glands, some of which measured up to 1·5 cm. in diameter. The spleen was firm, pale red, and weighed 28 g. The liver weighed 210 g. The anterior fontanelle was patent (1 × 0·7 cm.) and the posterior closed. The state of the dural venous sinuses was not recorded. Microscopy confirmed widespread bronchopneumonia, alternating with smaller areas of collapse. The enlarged cervical glands showed uniform lymphoid hyperplasia. Other somatic organs presented no noteworthy changes.

The Brain.—The brain was small, weighing 300 g. (normal 540 g.). This total included the cerebellum and brain-stem, which weighed 46 g. Although fluctuant on palpation, the meninges and gyri were externally normal. Extensive bilateral and approximately symmetrical cavitation was seen in the coronal blocks of the cerebral hemispheres (Fig. 1). The cavities varied in size from about 1 cm. in diameter to small, barely visible ones and some were obviously collapsed. Their lining was smooth, they contained clear, colourless fluid, and many were traversed by fine trabeculae, condensed in some areas, *e.g.*, the insula, into a dense, spongy network. The cavities were situated mainly in the deeper parts of the cortex and subjoining white matter. The cystic change was greatest near the anterior and posterior poles of the cerebral hemispheres where the only remaining solid tissue was irregularly shaped, ragged central islands of white matter. The temporal lobes were relatively well preserved, showing some demarcation between grey and white matter, and no cavitation except in their opercular portions. Save for the claustra, the basal ganglia were also intact, although their structural details were blurred, and the tissue was abnormally firm in consistency. The corpus callosum was thin, the fornices present, and the ventricles somewhat dilated. The brain-stem and cerebellum seemed small but otherwise normal.

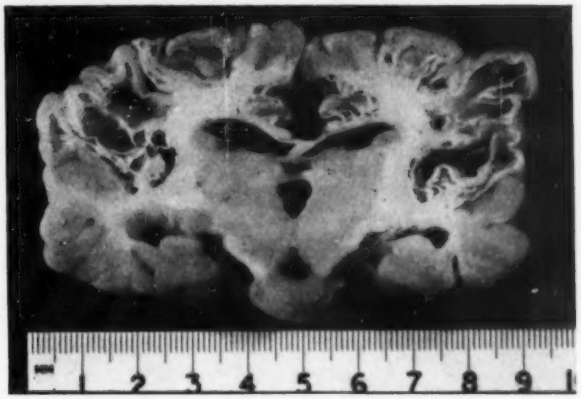

FIG. 1.—Coronal block of the brain.

After prolonged fixation in formalin many coronal blocks of the cerebrum and of representative parts of the brain-stem and cerebellum were embedded in paraffin. The extracerebral radicles of the great cerebral vein were dissected and removed as they emerged under the splenium of the corpus callosum and embedded separately. Sections were stained by the customary general and neurohistological methods, and frozen material was also used for staining fat and silver impregnation.

An obvious and striking histological change was partial obstruction of vessels in the subarachnoid space by plugs or collars of connective tissue. Some of these vessels were clearly veins or arteries, but many were atypical and it was often impossible to distinguish between them. The lesions were few, affecting on the average only two or three vessels or groups of vessels in a coronal section of an entire hemisphere.

All the affected veins were situated in the upper half of the supero-lateral and medial surfaces of the hemispheres (Fig. 2). The vessels varied in calibre: the largest were medium sized and the smallest

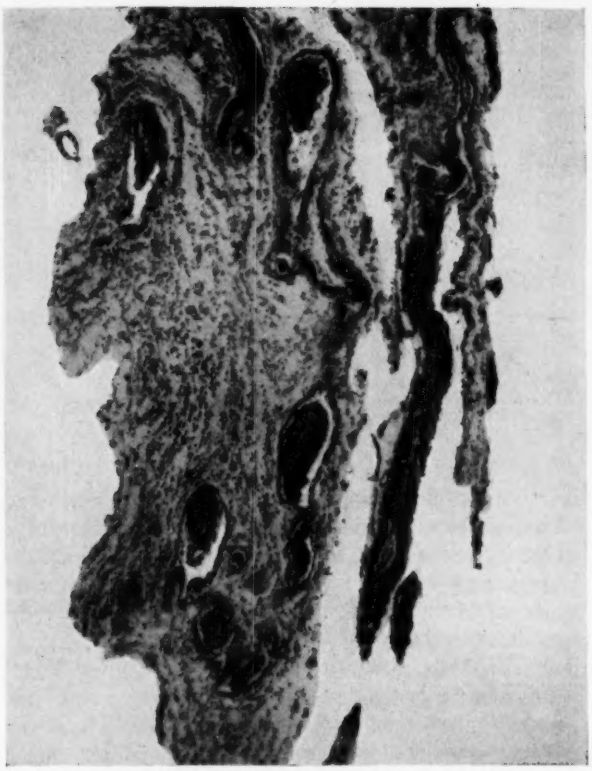

FIG. 2.—Obstructed veins in subarachnoid space. Haematoxylin and Van Gieson stain × 45.

FIG. 3.—Collagenized plugs with endothelium-lined spaces in veins. Haematoxylin and eosin × 190.

measured 50 to 60μ in diameter. While most were normally cylindrical, some showed localized dilatations with angular outlines. The occluding plugs consisted of densely arranged, parallel undulating fibres of fine collagen and reticulin with relatively few fibrocytes, and were mostly entirely or partly detached from the venous walls, thus lying freely or almost freely within the lumina of the vessels. Many contained single or multiple endothelium-lined channels (Figs. 3 and 4). A few elongated, spindle-shaped, cylindrical or polygonal particles of hyaline material, some of which showed slight peripheral calcification, were embedded in some of the fibrous plugs.

The branches of the great cerebral vein proved gritty and brittle on cutting, showing microscopically a thick, fragmented layer of hyaline partially calcified material adherent to the inner aspect of the venous wall. Where this layer was present, the remaining central part of the wall was retracted towards the lumen, thus presenting complete, or almost complete, mural reduplication. (The space between the outer and inner portion of the wall was empty and the retraction was, as in the case of the other obstructed veins, probably the result of

FIG. 4.—Venous plug showing retraction from vessel wall and recanalization. Haematoxylin and eosin × 190.

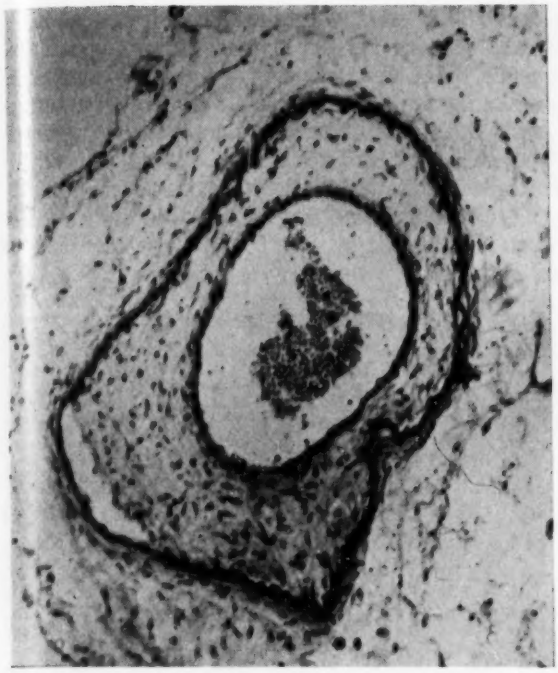

FIG. 5.—A collar of embryonic-like connective tissue in a small artery. Haematoxylin and eosin × 105.

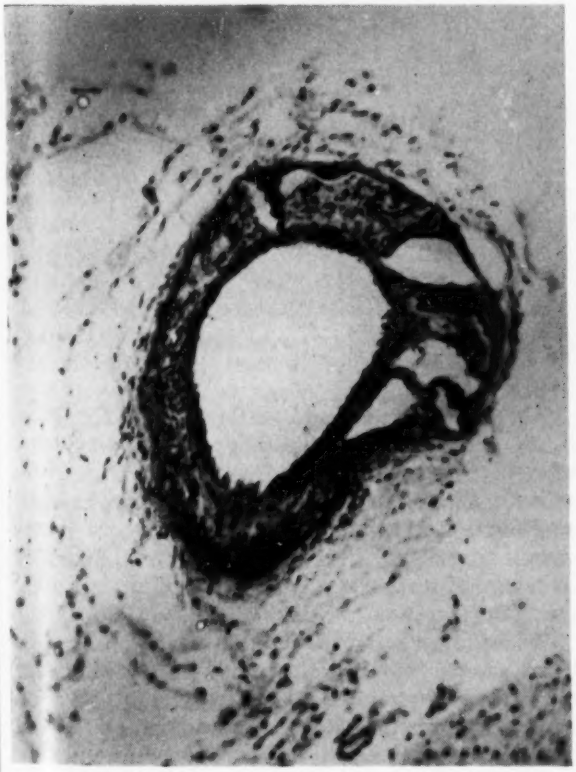

FIG. 6.—Artery showing fenestration in intramural collar of connective tissue. Haematoxylin and eosin × 105.

histological processing. No retraction was visible in frozen sections.) The detached inner portion of the wall was formed by connective tissue of irregular thickness and cellular density. The lumen was polygonal rather than circular in outline, retaining, however, good patency in all the sections examined.

Obstructed arteries were not as numerous as veins, but included among them a major branch of the middle cerebral artery in the Sylvian fissure. The affected arteries were identifiable by their conspicuous internal elastic laminae (Fig. 5). An annular layer of connective tissue was adherent to the inner aspect of the elastic lamina, which in some arteries showed partial calcification. Some collagen fibres were present in this tissue in the larger arteries. In others the connective tissue resembled closely embryonic mesenchyme, consisting of slender fusiform and stellate cells which formed a delicate, loose reticulum staining yellow with the Van Gieson technique and showing only a few indistinct reticulin fibres on silver impregnation by the Gordon and Sweets method. Some small granules of neutral fat were also present in this layer. Internally, around the patent lumen of the vessels, the connective tissue was condensed and collagenized in most of the affected arteries, showing also a few elastic fibres by appropriate staining. Unlike the venous plugs, the intra-arterial connective tissue showed little retraction towards the lumen, being fenestrated, however, by slit-like, empty clefts unlined by endothelium, in some of the larger vessels (Fig. 6). (This fenestration was also suggestive of the effect of histological processing on tissue of uneven density.)

Other changes in the subarachnoid space consisted of proliferation and dilatation of many of the unobstructed blood vessels. There was also focal increase of collagen and reticulin fibres with accumulation of phagocytic mononuclear cells containing neutral fat. No pigment, whether iron-containing or not, was seen in any part of the brain.

The cerebral tissue presented different stages of softening, resorption, cavitation, and gliosis. The lesions were situated under a strip of relatively well preserved cortex comprising in some areas only its outer laminae and in others its entire thickness. Whenever spared, the cortex showed only moderate astrocytic proliferation and the presence of scattered fat-laden microglial cells. Transition to the subjoining lesions was generally abrupt. These lesions consisted of cysts and solid tissue formed by varying proportions of fat-laden cells and protoplasmic and fibrous astrocytes (Fig. 7). In some areas fat-laden cells were very numerous and dense, particularly around blood vessels. In paraffin-embedded material these areas resembled adipose

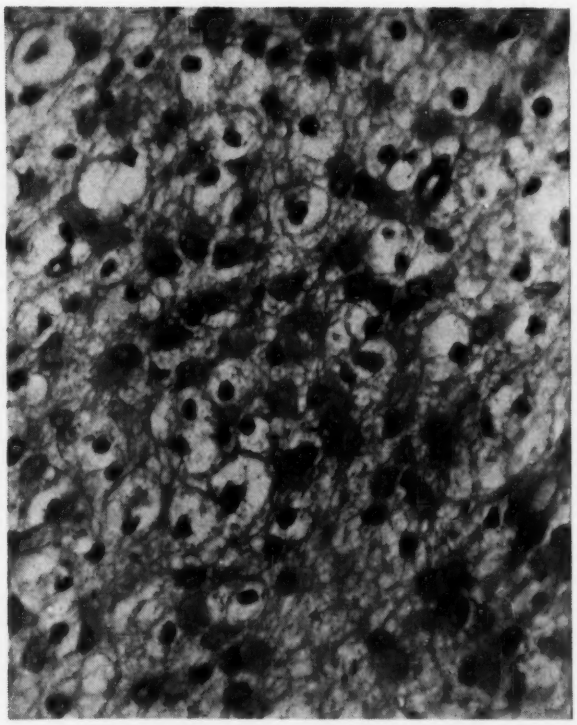

FIG. 7.—Solid tissue formed by a mixture of protoplasmic and fibrous astrocytes with many vacuolated microglial cells. Haematoxylin and eosin × 420.

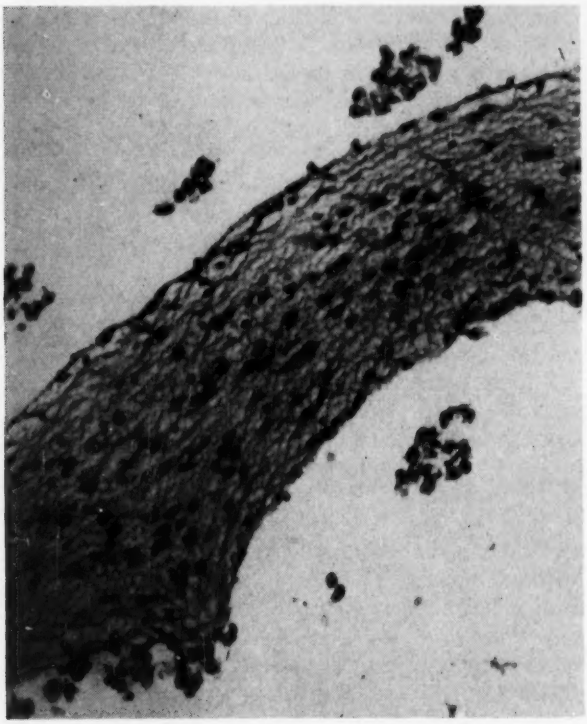

FIG. 8.—Trabeculum formed by protoplasmic and fibrous astrocytes. Phagocytic, fat-laden cells are seen in the adjoining cysts. Haematoxylin and eosin × 190.

tissue. They stained bright red with scarlet R. in frozen section and contained many anisotropic crystals. In some areas protoplasmic astrocytes were more numerous, and in others, fibrous astrocytes. The cysts contained some fat-laden phagocytic cells and their trabeculae were formed by protoplasmic and fibrous astrocytes (Fig. 8).

No inflammatory change or evidence of a past or recent haemorrhage was found anywhere in the brain.

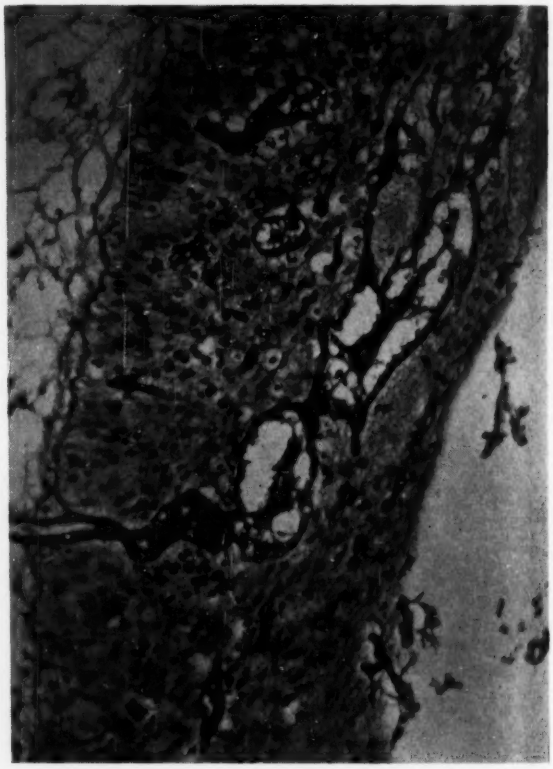

FIG. 9.—Irregularly formed intracerebral vessel. Gordon and Sweets method × 135.

All intracerebral blood vessels seemed free from intramural obstruction and bore no direct evidence of past or recent thrombosis. Sections stained for reticulin showed, however, widespread focal vascular proliferation with marked irregularity of many vessels, consisting of mural duplication, localized distention, tortuosity, and thickening of their reticulin framework (Fig. 9).

With the exception of the destroyed claustra, the basal ganglia were relatively spared, showing only moderate neuronal loss with astrocytic proliferation and a few small foci of incomplete softening. Marked glial proliferation was present around the ventricles.

Few myelinated fibres could be demonstrated in and around the cerebral lesions and in the surviving

areas of the cortex. These showed ballooning, beading, fragmentation, and unevenness of staining. Axon cylinders in Bielschowsky preparations seemed more numerous. The internal capsules were also poor in myelin fibres, but their number was greater in the lower part of the basal ganglia and in the brain-stem. The pyramidal tracts were rudimentary. Although no special study of myelination was made against normal controls, the development of tracts, other than cortico-fugal, appeared to be consistent with the age of the subject (Flechsig, 1920).

The brain-stem was substantially normal, presenting only slight diffuse and marginal astrocytic hyperplasia. The cytoarchitectonic structure of the cerebellum was also normal, but some Purkinje cells were pyknotic and shrunken. Moderate cellular and fibrous gliosis was present in the cerebellar white matter, and in this area some of the myelin fibres showed beading and fragmentation.

Discussion

Cerebral changes comparable with the above but not associated with vascular involvement have been reported by Sternberg (1930), Brocher (1932), Diamond (1934), Ford (1937), Winkelman and Moore (1942), Marburg and Casamajor (1944), Lumsden (1950), by Negrin, Lepow, and Miller (1952), and by Kramer (1956). Marburg and Casamajor thought that the condition was caused by venous thrombosis or functional " venostasis ", possibly initiated by birth injury. One of their cases (Case 1) showed in fact a few venous thrombi, but these were clearly of recent antemortem origin and could not have accounted for the older cerebral lesions. Like most workers, Lumsden failed to find any vascular lesions after a careful examination of his material and birth injury was also improbable in his well documented case. He concluded that infantile encephalomalacia does not necessarily indicate past infarction but may be also the result of many other causes, such as infection, toxaemia, and degeneration. He suggested further, as a hypothesis, that important factors in the pathogenesis of the condition were the far greater degree and speed of transynaptic degeneration of infantile as compared with adult neural tissue, and its greater vulnerability to autolytic enzyme action.

Vascular lesions, arterial or venous, are, on the other hand, very familiar as an important cause of many forms of infantile cerebral cavitation and gliosis. Such lesions have been described, for example, by Byers and Hass (1933), Bailey and Hass (1937), Stevenson and McGowan (1942), Altschul (1949), and more recently by Bertrand and Bargeton (1955), Norman and Urich (1957), and Norman, Urich, and McMenemey (1957). These vascular lesions did not resemble, however, those in the present case. The patients were mostly older, cavitation and gliosis showed different localization, being also histologically more uniform in any one instance and lacking the pleomorphism of the present case.

Nevertheless, a few cases comparable with the present have been recorded. Thus in one reported by Wohlwill (1921) pial arteries showed proliferation of subendothelial connective tissue. Cavitation was confined, however, to the cerebral cortex of one hemisphere. The white matter was sclerosed but not cystic. In another case described by Levin (1936) calcification and mural thickening of pial arteries was associated with widespread and allegedly progressive multifocal softening of the cerebral cortex. Only one small cystic lesion was found in the white matter. Veins in the above two cases were intact.

Three cases reported by the Hungarian workers, Juba (1936) and Cseh (1937), bore an even greater resemblance to the present one. The brain of Juba's first case showed similar subendothelial proliferation of connective tissue in the pial arteries over both occipital lobes, the subjoining grey and white matter being the seat of " progressive " cavitation and gliosis. Juba's second case showed more widespread changes. In some vessels the subendothelial connective tissue had undergone hyaline degeneration while concentric new layers of the internal elastic lamina had been formed in a few arteries. Cseh's case was a child born after a normal confinement who developed early severe epilepsy and suffered from spastic paralysis with general retardation of development. He died aged 14 months. The brain weighed 220 g. and showed extensive cystic degeneration in varying stages of softening, resorption, and gliosis. Changes in the pial arteries were again closely similar to those of the present case. No venous lesions were demonstrated in any of the above three cases.

In a further instance mentioned by Meyer (1948), apparently identical vascular and neural changes were found in an infant aged 3½ months. It is not clear from Meyer's account whether both arteries and veins were involved. The author thought that the lesions indicated preceding thrombosis. In a later joint review (Hallervorden and Meyer, 1956), the above case was referred to again, the authors stating that the commonest cause of such thrombosis was neonatal asphyxia but citing no further evidence in support of this view. This opinion was contrary to that of Juba and Cseh, who did not regard thrombosis as a possible mechanism in their cases.

Unlike the earlier cases, the present one showed a combination of both arterial and venous lesions. While it is difficult to interpret the arterial changes,

most of the venous lesions appeared to exemplify the usual process of organization, collagenization, and recanalization of old thrombi. Since little is known about the evolution of arterial thrombotic lesions originating before or soon after birth, it would be unreasonable to exclude the possibility that both venous and arterial changes were caused in a like manner, *viz.*, that they were thrombotic in origin.

The tentative diagnosis of haemorrhagic disease and intracranial bleeding made in this case was not substantiated by the pathological findings. It is tempting to assume a causal relationship between the neonatal asphyxia and the encephalopathy. Recognizable birth injury or neonatal distress were absent, however, in many of the previously recorded similar cases of cystic encephalomalacia with or without vascular involvement. It is also impossible to disregard their striking resemblance to swayback in lambs, which is probably of antenatal origin (Innes and Shearer, 1940).

A further problem is the disparity between the considerable extent of the neural changes and the relative sparseness of the vascular lesions. This may be explained, perhaps, by postulating the additional operation of histologically undemonstrable functional circulatory disturbances (Levin, 1936; Marburg and Casamajor, 1944) and/or the compensatory development of new vascular channels following obstruction of older ones. It is also possible that some thrombi may be resorbed without trace. Vascular lesions were, however, entirely absent in the majority of similar cases, and the reason for the cavity formation in these remained unknown. The already mentioned hypothesis of Lumsden may provide, after testing, an answer to this problem.

Summary

The brain of an infant, who had had severe neonatal asphyxia and died aged 3½ months, showed extensive symmetrical cystic multilocular encephalomalacia. Some of the veins of the subarachnoid space were obstructed by partially recanalized plugs of connective tissue. The main radicles of the great cerebral veins showed thickening and focal mural calcification. Some arteries in the subarachnoid space were also obstructed by an intramural collar of embryonic-like connective tissue. The literature relating to this condition is reviewed. The vascular changes were tentatively interpreted as organization of old thrombi.

I am indebted to Mr. C. L. Bourne for supplying the obstetric details of the case, to Drs. J. W. Platt and S. Yudkin for the clinical notes, and to Dr. P. W. Darby for placing the material and post-mortem notes at my disposal. Professors P. M. Daniel and C. E. Lumsden have kindly examined and discussed with me the histological sections. My colleagues at the Fountain Hospital read and criticized the manuscript of this paper.

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BOOK REVIEWS

The Vertebrate Visual System. By S. Polyak. £16 17*s.* 6*d.* Chicago: University of Chicago Press. (London: Cambridge University Press.) 1957.

This work is a remarkable monument to the author, who died in 1955 after the task was largely completed, but his friend Professor Klüver was obliged to devote two years' work on the manuscript before it was finally seen through the press.

The historical aspects were a special interest to the author, and this book contains more than a hundred portraits of those who have contributed to the study of optics and vision.

Like the forerunner of this work, *The Retina*, there is special emphasis on anatomical structures as they occur throughout the animal kingdom. His book on *The Main Afferent Fibre Systems of the Cerebral Cortex in Primates* (1932) is also incorporated in this volume.

Part 4 contains some fascinating chapters on the biology of the visual system in vertebrates, and on the importance of vision in the evolution of man himself.

The beautifully illustrated anatomical chapters in Part 2 occupy over 400 pages, and constitute a fine record of research.

Consideration of the pathological appears in Part 3, and is concerned mainly with a description of those conditions which illustrate or contribute to anatomical knowledge. Thus lesions of all parts of the visual system which can be studied by perimetry receive special attention. This part is disappointing in that it is out of date in its discussion of macular representation and does not consider some of the higher forms of visual disorder such as those which lead to inattention or disorientation in hononymous half fields.

Finally a bibliography of 10,000 references completes this massive life's work, and ensures that if only as an indispensable work of reference, the monument is well and truly built.

Metabolism of the Nervous System. Edited by Derek Richter. (Pp. xiv + 600; illustrated. 100*s.*) London: Pergamon Press. 1957.

This volume reports the proceedings of the Second International Neurochemical Symposium held in 1956. No clinical neurologist can fail to find some part of it of the greatest interest. Biochemistry is becoming increasingly obtrusive in neurology. The outpost skirmishes of the toxic neuropathies and the mechanism of thiamine deficiency in the nervous system are now leading on to more central problems such as the detailed chemical processes of demyelinization in multiple sclerosis and, inevitably, of its corollary the formation and maintenance of normal myelin. The biochemical implications of such systemic diseases as primary sensory neuropathy, motor neurone disease and, more particularly, of hepatolenticular degeneration, are also becoming clearer. The further step to the fundamental cytochemistry of the neurone has long ago been taken by biochemists, and it is mainly with such basic scientific work that this book deals. It is good to know that inhibitory processes are continuing to occupy the interest and attention of biochemists as well as neurophysiologists. The chapter on non-cholinergic transmission gives an excellent review of the trend of work and interpretation in this field. The clear recognition of an inhibitory transmitter substance of any general neural application would hardly fail to have almost immediate clinical importance in the fields of neuropsychiatry and epilepsy, if nowhere else. One section included in this volume, though not strictly biochemical, was of particular interest to this reviewer—that on electron microscopy of nervous tissue. The picture revealed of the submicroscopic structural organization of both nerve fibres, nerve cells, and synapses is one of increasing complexity. These structural findings are beginning to catch up with the equally complex functional changes, electrical and otherwise, which are known to accompany the activity of neurones. Although this book is not in any way concerned with clinical problems, many points arise which have potential clinical application, if only by stimulating a fresh interpretation of some symptoms and signs in neurology.

Progress in Neurobiology: II. Series Editors: Saul R. Korey and John I. Nurnberger. **Ultra Structure and Cellular Chemistry of Neural Tissue.** Edited by Heinrich Waelsch, with 37 participants. (Pp. xv + 249; 40 figures. 57*s.* 6*d.*) London: Cassell; New York: Hoeber. 1957.

The contents of this symposium are admirably described by its title. Professor J. D. Robertson deals with the electron microscopy of neuronal membranes, with special reference to the myelin sheath. Professor Palay describes the fine structure of the neurohypophysis. Both articles are illustrated with excellent photographs. Professor Lowry describes some of his work on the determination of the activity of various enzymes in single nerve cells. Working on a somewhat larger scale, Professor Robins and his colleagues have assayed some of the important enzymes concerned in glucose breakdown in the various layers of the cerebellar cortex; these results are relevant to an assessment of the relative importance of the Embden-Myerhof pathway and of the more recently elaborated hexose-monophosphate shunt. Histochemistry is represented by Professor Koelle and Professor Gomori who deal chiefly with the localization of cholinesterases in neurones and sympathetic ganglia. Professor Bain discusses the uncoupling of oxidation phosphorylation in brain mitochondria by barbiturates; the point of attack has been more precisely localized since this contribution but the relevance of the effect to the

clinical actions of the barbiturates remains uncertain. Dr. R. S. Geiger's studies on the growth (and mitosis) *in vitro* of what are almost certainly neurons, taken from the cortex of adult monkey and man are of considerable interest. So also is the article by Professor Numberger and Dr. Gordon in which they have determined the proportion of neuronal to non-neuronal cells in various parts of the rat brain.

It will be seen that a wide range of topics is covered and this book contains much that is of interest. The amount of space (about 60 pages) devoted to the discussions which followed the presentation of the various papers seems disproportionately high.

The Human Brain: From Primitive to Modern. By A. M. Lassek. (Pp. viii + 242. 36*s*.) Oxford: Blackwell Scientific Publications. 1957.

Professor Lassek is well known for his anatomical and histological studies of the mammalian nervous system and especially for his work on the pyramidal tracts and their functions. In this book, however, he is more speculative and philosophical. In the first 10 chapters, which constitute less than a third of the book, he reviews in very general terms the evolution of the structure and basic physiological functions of the brain. The remaining chapters are concerned with the evolution of mind considered in a broadly anthropological framework. Such a large canvas inevitably leads to a rather impressionistic approach; and the result is unlikely to be of much value either to the scientific student of the brain and its functions or to the trained philosopher. Psychology students may, however, find it a useful introduction to the inter-relationship of mind and brain.

Pathologische Histologie des Peripheren Vegetativen Nervensystems. By Heinz Hermann. (Pp. 126; 50 figures. Price not stated.) Berlin: Berliner Medizinische Verlagsanstalt G.m.b.H. 1956.

This book is an account of the morphological appearance of the various components of the autonomic nervous system in many widely different pathological conditions ranging from inflammation to psychiatric disease. They are based on material impregnated with silver and prepared with the techniques advocated by Stöhr and his school. It contains 50 illustrations of which only nine are photomicrographs (of poor quality); the rest are elaborate drawings containing details which it is hard to believe could have been resolved with a light microscope.

The various components of the autonomic nervous system are dealt with separately. There is a short description of their " normal " appearance followed by a description of their appearance in a variety of tissues which are the seat of pathological changes.

Unfortunately, the author supplies few quantitative data in support of his arguments. In the first place, he admits that the technique he uses is difficult to handle and that up to 12% of ganglion cells appear to be undergoing degenerative changes in the absence of disease. In pathological conditions, up to 85% show degenerative changes. His criterion of what constitutes degeneration is not based on any experimental evidence and he apparently takes no account of technical artefacts or post-mortem changes. It is possible, for instance, that some of the characteristic morphological alterations which he describes take place after death and are not due to the particular pathological process under investigation. Such a possibility must be excluded before it is permissible to conclude with the author that widespread degenerative changes seen in parts remote from the lesion are evidence that the autonomic nervous system is a syncytial protoplasmic reticulum.

This is not to say that Professor Hermann's book serves no useful purpose. There can be little doubt that he has demonstrated that the autonomic nervous system undergoes morphological change, but he has as yet not supplied sufficient data to connect these changes with any specific pathological process.

Précis de Biologie Humaine: Les bases organiques du comportement et de la pensée. By Paul Chauchard. (Pp. xii + 403; 59 figures. Fr. frs. 1,400.-.) Paris: Presses Universitaires de France. 1957.

Dr. Chauchard is well known as a prolific writer on physiological and medical topics. Although much of his work has been avowedly semi-popular, the present book is intended as a more serious introduction to human biology. After giving some account of modern work on heredity and constitution, the author considers at some length the relationship between neural and endocrine mechanisms in the control of behaviour. He then passes on to a detailed exposition of cerebral function as seen principally from the psychological standpoint. There is a final short section on the " physiology of conduct ", in which problems of appetite, instinct, and social organization find mention. The text is embellished by a number of informative, if somewhat messy, line drawings.

Although Dr. Chauchard is clearly well acquainted with contemporary neurological inquiry, his book cannot be said to break new ground. Even as a text for students, it is both less complete and less critical than Morgan and Stellar's " Physiological Psychology ", which has long been available in French translation. None the less, this book will be welcomed as an able and scholarly contribution in the tradition of Ribot, Piéron, and Fessard.

Selected Writings of Walter E. Dandy. Compiled by Charles E. Troland and Frank J. Otenasek. (Pp. vii + 789; illustrated. 112*s*. 6*d*.) Oxford: Blackwell Scientific Publications; Springfield, Illinois: Charles C. Thomas. 1957.

This book of his selected writings is in some ways a commentary on Walter Dandy, Dandy was an excellent craftsman—probably more dextrous than his half-acknowledged master, Harvey Cushing. This led him to a more radical brain surgery than Cushing: and in his hands the radicalism almost always paid dividends. His contributions were, in general, improvements in technique rather than anything more fundamental. However, a certain impatience with the diagnostic results, and particularly the localizing value for cerebral lesions, of a formal clinical neurological examination led him to develop the procedure of air ventriculography and its derivative air encephalography, and here he certainly added a fundamental diagnostic procedure to neurology.

His studies of cerebrospinal fluid formation and absorption, though probably stimulated in part by the practical problems of hydrocephalus, were also a basic physiological contribution. Dandy was an excellent clinical observer and recorder—alert and shrewd. Before the modern interest in intervertebral disc surgery was under way, he had observed and recorded central disc protrusion and its possible causative role, both in bilateral sciatica and in spinal block. His paper on inflammatory tumours of the spinal epidural space also clarified much previous confusion and remains an excellent source of clinical information. When he started to theorize, however, his weaknesses became apparent. Thus his views on the aetiology of Menière's syndrome and, particularly on the cerebral seat of consciousness have a rather naïve and old-fashioned ring about them. The papers selected in this book illustrate all these points.

His quarrel with Cushing was notorious in its day. He claimed that it started when as Cushing's assistant in 1913 experimental results he was getting on glycosuria and the autonomic system were contradictory to what Cushing had postulated. Real bitterness came, however, when he published a preliminary note in 1921 about radical extirpation of acoustic neuromas and Cushing accused him of failing to acknowledge his own earlier work. It was a storm in a teacup—the clash of two personalities, both able and ambitious men. It is reflected indirectly in this volume. Before 1913 Cushing is always thanked in the " acknowledgements " of Dandy's papers; after this year his name appears no more.

The Neurologic and Psychiatric Aspects of the Disorders of Aging. Association for Research in Nervous and Mental Disease Research publication. (Pp. ix + 307; 79 illustrations, 17 tables. 68*s*.) London: Baillière, Tindall & Cox; Baltimore: Williams and Wilkins. 1956.

This volume is slim compared with many in this series. Its size represents a paucity of information on the subject reviewed. Some of what is reported is trivial, some anecdotal, and some only the obvious extension of well-known pathological processes to the conditions of the senium—as Critchley puts it, a study of the *senium ex morbo* rather than the *senium naturale*. There is little fundamental observation—either laboratory or clinical—discussed, and small evidence in this book at any rate that such fundamental work is being undertaken. However, Warren Andrew's review of structural alterations in the ageing nervous system does give a glimpse of interesting histological and cytochemical changes and the possibilities they suggest for further work. Pope, Lunsford, and McCay's essay on experimental prolongation of the life span also mentions some potentially interesting experimental work on parabiosis in animals though the work hardly seems advanced enough yet to justify reporting. Lorge casts some doubt on the widely held view that learning ability decreases with age. Perhaps one of the most disappointing lacunae is in the genetic study of the disorders of old age and its related healthy longevity.

Schizophrenia: Somatic Aspects. Edited by Derek Richter, Neuropsychiatric Research Centre, Cardiff. (Pp. viii + 180; illustrated. 40*s*.) London: Pergamon Press. 1957.

These papers were presented at a meeting held in London in 1956. The contributors survey the present position of our knowledge of schizophrenia from the standpoint of habitus, heredity, electroencephalography, biochemistry, morbid anatomy, endocrinology, and phamacology. The editor points out in his modest foreword that this collection of viewpoints is not intended to be comprehensive, and adds, rather needlessly, that the book is not a final account of the results of research. It is pleasantly written and produced, but contains little that is not accessible in other compilations of the same type.

Symposium International sur la Psychothérapie de la Schizophrénie, Lausanne, October 1956. Reports and discussions, edited by G. Benedetti and C. Müller. (Pp. 264; 4 figures. S.Fr. 35.-.) Basel: Karger. 1957.

Although Freud consistently deprecated the treatment of psychotic illness by psychoanalysis, there has been an increasing readiness to experiment in this direction. The symposium reported here testifies to the spread of this trend to Switzerland, Germany, and France. It is tinctured with existentialism, and the exposition is correspondingly difficult to follow. It suffers also from the indifference which the contributors show to the need for supplying evidence that the treatment was beneficial. Individual cases are reported, with elaborate—and sometimes contradictory—interpretations of the psychopathology but without any demonstration that the treatment was responsible for whatever improvement occurred: the emphasis is often far more on philosophical than on medical issues. The reader will quickly discover, by his response to Professor Benedetti's introductory review, whether this line of inquiry and discussion is congenial to his thinking.

Psychotherapy: A Modern Theory and Practice. By E. Lakin Phillips. (Pp. xviii + 334. 30*s*.) London: Staples Press. 1957.

It is refreshing to meet an exposition of psychotherapy which is not a variation on the psychoanalytic theme. Dr. Phillips bases his method on a theory of learning, and seeks to " interfere " with the patient's choice of probabilities in his daily life. He does not concern himself with unconscious influences and happenings: " We do not set up mind-structure so formidable that it has to be beaten down or broken into a defenceless position, or plumbed to its depth." Dr. Phillips restates, in accordance with his theory, many of the processes involved in falling neurotically ill and in getting well, and he illustrates his " interaction " procedure with protocols of therapeutic interviews, which make it evident that the therapist has to work hard and do most of the talking. Direct and economical as his treatment seems to be, it is by its success in action that it must be judged: and here Dr. Phillips has as yet little to offer us beyond reports of recovery in individual cases, which leave us where we were. Because of its fresh approach and its sustained effort to make use of recent research in

psychology and communication theory, the book deserves attentive reading.

La Thérapeutique par la Chlorpromazine en Pratique Psychiatrique. Edited by L. Revol, with a Preface by Professor Henri Ey. (Pp. 154. Fr. frs. 800.-.) Paris: Masson. 1957.

The French chemists to whom we owe chlorpromazine have seen this substance rapidly become one of the most-employed drugs in psychiatry, while its mode of action and the indications for its use are still obscure. French psychiatrists have been foremost in recording their enthusiasm, and Professor Revol and his colleagues at Lyons and Chambéry are able in this manual to cite a considerable literature, mainly French. The treatment of the theme is in three sections: the first briefly recounts the history and what is known of the pharmacology of the drug; the second recounts the psychiatric illnesses for which it has been found effective; and the third describes the manner of administration, the dose, duration of treatment, complications, and contraindications. As a practical statement of French clinical experience the manual is informative, but it contains no records of clinical trials properly carried out, and cannot be regarded as a serious contribution to the assessment of this remarkable substance.

Psychiatrie Pratique. By Roger Coulonjou, with a Preface by Professor Lhermitte. (Pp. 254. Fr. frs. 1,850.-.) Paris: G. Doin. 1957.

Written for the general practitioner, the book contains nothing profound or new. It is amiably receptive towards ideas lately in fashion regarding such matters as psychosomatic medicine and the effects of separating a child from its mother; and it points out robustly that existing psychiatric textbooks are too long and obscure. Dr. Coulonjou is a former pupil of Professor Lhermitte, who writes a lively foreword, putting the psychopathologists and psychotherapists in their place, and exalting the factual or somatic approach to mental illness. On the whole the book fulfils its modest purpose, and incidentally shows that French psychiatry has been assimilating itself rather fast to that now current in America, without wholly sacrificing its distinctive excellence in clinical description and analysis.

La Psychanalyse d'aujourd'hui. Vols. I and II. (Published under the direction of S. Nacht, with Preface by E. Jones. (Pp. 867. Fr. frs. 2,800.-.) Paris: Presses Universitaires de France. 1956.

The 23 psychoanalysts who have collaborated in producing this compendium have had a difficult task; psychoanalysis is not an orderly body of knowledge which can be parcelled out between a score of writers without risk of repetition and serious omission. Dr. Nacht has coped with these problems with some success, and he has taken advantage of the fact that French psychoanalysts have limited themselves mainly to clinical and technical aspects. The opening article by himself and Dr. Lebovoci exemplifies this practical bias: it deals with the indications and contraindications for undertaking the psychoanalysis of adults. The other articles in the first volume deal with psychopathology and treatment, especially in childhood and adolescence; and with sexual abnormalities and the relation between psychoanalysis and medicine.

The second volume begins with a disappointing chapter by Ajuriaguerra, Diatkine, and Badaracco on psychoanalysis and neurobiology. Ensuing chapters are concerned with analytical treatment of psychoses, critically expounded by Racamier; psychosomatic medicine; prevention; sexology; and surveys of the development of psychoanalysis and its literature.

The psychoanalysts in France have been fewer than in England and the United States, and dissensions among them have been more recent, though not more unsettling, than in other countries. This work of multiple authorship, sponsored by the official Institute of Psychoanalysis, indicates that they are entering on a phase of consolidation along orthodox lines.

Kraepelin und Freud. Beitrag zur neueren Geschichte der Psychiatrie. By Kurt Kolle. (Pp. 88. DM. 7.60.) Stuttgart: Georg Thieme. 1957.

It is a pious duty which Professor Kolle fulfils in writing of his great predecessor in the Chair of Psychiatry at Munich. It is less easy to see why he has chosen to write also of Freud, a man of entirely different outlook. Though contemporaries, these two men, Kraepelin and Freud, had irreconcilable views of how the study of mental disorder could be advanced. Professor Kolle's efforts to reconcile or combine them results in a woeful dilution which they would hardly themselves have sanctioned. He regards Kraepelin's achievement as having consisted largely in the development of a durable nosological system: he does not draw sufficient attention to Kraepelin's contributions to abnormal psychology, pharmacology, and cultural psychiatry. What he says of psychoanalysis is along conventional lines: he praises Freud's originality and courage in inquiry, he selects those parts of the Freudian theory and practice which he finds satisfactory, and passes lightly by those fundamental tenets of psychoanalysis which the non-analyst can hardly bring himself to accept. The book is a convenient index of the changing climate in German psychiatry.

L'Elettroencefalografia Clinica. By Carlo Perris. (Pp. 264. L. 2,500.) Pisa: Edizioni "Omnia Medica". 1957.

This monograph deals almost entirely with the electroencephalographic changes in focal cerebral lesions, particularly tumours. As the value of clinical electroencephalography is increasing in recognizing and locating focal lesions, whether or not they give rise to epilepsy, the book is timely. It gives a detailed description of the methods and techniques used for such localizing work, mentions all the common provocative techniques, and provides an excellent review of the literature, with full references up to the year 1954.

In the second and smaller part of the book the author reviews his own experiences with 80 cases of cerebral tumour. This serves to illustrate and emphasize the various points made in the first part.

Altogether, this is a useful short introduction to the

electroencephalography of focal lesions. The language difficulty need not deter the English reader of reasonable intelligence and with a knowledge of E.E.G. terminology, as most of the technical words are but thinly veiled in their Italian transliteration.

The Epileptic Seizure. A Clinical-Electrographic Analysis of Metrazol-induced Attacks. By Cosimo Ajmone-Marsan and Bruce L. Ralston. (Pp. xii + 251; 45 figures, 30 charts. 45*s*.) Oxford: Blackwell Scientific Publications; Springfield, Illinois: Charles C. Thomas. 1957.

This monograph records the effects of the injection of metrazol in epileptic subjects. The changes seen in the patient and his electro-encephalogram are used to localize the site of the discharging lesion and to study the behavioural accompaniments. The work is by a team in a research institute where patients are subjected to special and highly specific study, and the data have not necessarily direct application to the care of the epileptic patient at large. The method of " activation " the authors use is effective and safe, but the phenomena produced are exceedingly complex and their description and analysis seems to be somewhat tortuous.

DENIS WILLIAMS

Epileptic Seizures. Edited by John R. Green and Harry F. Steelman. (Pp. xii + 168, with frontispiece and 17 illustrations. 40*s*.) London: Baillière, Tindall & Cox; Baltimore: Williams & Wilkins. 1956.

This book is the result of a joint meeting of the Western Institute of Neurology, the Western Society of Electroencephalography, and the American Academy of General Practice. It is divided into three parts. The first is concerned with diagnosis, the second with treatment, and the third with educational and social problems. This last section reflects the general social environment of the United States and is only applicable in very general terms to this country. It is evident that the major problem there, as here, is to get the community in general to accept and allow for the epileptic. Some useful information is given about disposal problems and the way they are overcome both for special cases such as cerebral palsies with epilepsy and for the " normal " epileptic of average education.

Diagnosis is considered both clinically and electrically. A useful brief analysis of clinical fits and their site of origin is given by Wilder Penfield. Electroencephalographic localization is also reviewed. Medical and surgical treatment is discussed. Anticonvulsant drugs are being developed rapidly, and several that are now proving useful in 1957 are not mentioned in this book published in 1956. The late results of surgical treatment —cortical excision of epileptic foci—are reviewed by Penfield and suggest that 40-45% are free from attacks for a seven-year follow-up period. In general the book reflects the modern approach to epilepsy in which the " causes " of the condition are put on one side and the practical problem is regarded as one of finding where the epileptic discharge originates and then of stopping it by medical or surgical means. It is a useful short summary of this attitude and can be recommended to students and practitioners.

Épilepsie: Étude Clinique, Diagnostique, Physiopathogénique et Thérapeutique. By J.-A. Chavany; Foreword by Prof. Petit-Dutaillis. (Pp. 356; 24 figures. Fr. frs. 2,800.-.) Paris: Masson. 1958.

This book approaches epilepsy mainly from the clinical standpoint. In the first part the epilepsies are classified clinically and the symptoms and signs analysed; an anatomical classification is, however, also introduced, as some attempt is made to indicate the likely site of the origin of the particular form of seizure being discussed. Part two considers special aspects of epilepsy, such as status, mental changes in epilepsy, suicide, and a variety of clinical subgroups—sleep epilepsy, myoclonic epilepsy, infantile epilepsy, and reflex epilepsy. A third part considers diagnosis with special emphasis on the E.E.G., and finally, a fourth, anatomy and physiology, together with treatment.

In general, most of the facts are there, but the book is badly arranged, so that information is repeated and there is no method of distinguishing what is important from what is trivial. Certain authors are mentioned by name in the text, but no attempt is made to provide proper references.

Mental Deficiency. By L. T. Hilliard and Brian H. Kirman. (Pp. xvi + 517; 90 figures. 60*s*.) London: J. & A. Churchill. 1957.

The concept of mental deficiency has been gradually changing in the past few decades from an assessment based mainly on " intellectual " tests to one based more on " social efficiency ". This has been a most valuable and productive change of attitude, and it is reflected in this book. The idea that mental deficiency has as its aetiological background functional abnormalities in the biochemical and physiological spheres has also gained ground, though it was always recognized implicitly by workers in this field. Here, too, this new book reflects the new emphasis. It is, moreover, an essentially practical book, and deals adequately not only with the management of defectives in health and disease but with the legal and social aspects of the problem also. A useful chapter on advice to parents is included. The book can be thoroughly recommended to students and practitioners who want an up-to-date, practical and humane introduction to the subject. The British literature in this important field is small, and this is a most worth-while addition.

Hospital Treatment of Alcoholism. By Robert S. Wallerstein and Associates; Introduction by Karl A. Menninger. (Pp. x + 212. $5.00.) New York: Basic Books. 1957.

This is a study of 178 chronic alcoholics, treated as in-patients in one of four different ways—by " antabuse " therapy, conditioned reflex therapy, hypnotherapy, and " milieu therapy ". The latter was intended as a control group having the same hospital facilities as the other groups (activity programme, group and individual psychotherapy, *etc*.) without any of the " specific " therapies. It became clear, however, that this group evolved as a distinct treatment group. The authors studied not only the overall results of the different

therapies, but also endeavoured to ascertain which types of patient did best with the different methods of treatment.

The results bore out the opinions of most clinicians, namely, that the treatment of the chronic alcoholic is not very satisfactory. Only "antabuse" gave better results than the "milieu therapy" group. The results with conditioned reflex therapy (emetine) were no better than in the "milieu therapy" group. One wonders, however, whether the conditioned reflex therapy was given in its most effective form. The treatment was given once daily for five days; perhaps a more concentrated form of induced emesis, reducing the patient to the state of physical and mental exhaustion which Sargant has described, when the patient is more receptive to ideas of "conversion", would have given better results.

This is a careful, if pessimistic, study which should be read by anyone interested in the treatment of the chronic alcoholic.

BOOKS RECEIVED

(Review in a later issue is not precluded by notice here of books received.)

Les Accidents circulatoires du Cerveau: Traitement Chirurgical de L'Hémorraghie et de L'Ischémie. By J. Guillaume, G. Mazars, R. Rogé, and A. Pansini. (Pp. viii + 141; illustrated. Fr. fr. 1,600.-.) Paris: Presses Universitaires de France. 1957.

Les Méningiomes: Étude Clinique et Chirurgicale. By J. Guillaume, R. Billet, J-P. Caron, and D. Cucca. (Pp. vii + 173; illustrated. Fr. fr. 2,700.-.) Paris: Presses Universitaires de France. 1957.

Mental Seduction and Menticide. The Psychology of Thought Control and Brainwashing. By Joost A. M. Meerloo. (Pp. 324. 21*s*.) London: Jonathan Cape. 1957.

Anatomie schématique de L'Appareil Nerveux. **Systematisations des Centres Nerveux et de leurs Connexions.** By R. M. de Ribet. (Pp. 1050; 385 figures. Fr. fr. 7,200.-.) Paris: G. Doin. 1957.

Methods of Group Psychotherapy. By Raymond J. Corsini. (Pp. xi + 251. 49*s*.; $6.50.) New York, Toronto, London: McGraw-Hill. 1957.

Deafness, Mutism and Mental Deficiency in Children. By Louis Minski. (Pp. viii + 82; 13 figures. 12*s*. 6*d*.) London: Heinemann. 1957.

L'Enfant inadapté: Rôle medico-social du Médecin. By L. Michaux and D. J. Duché. (Pp. 361. Fr. fr. 3,600.-.) Paris: G. Doin. 1957.

Hypnosis in Health and Sickness. By Gordon Ambrose and George Newbold. (Pp. 196. 15*s*.) London: Staples Press. 1957.

Chemotherapy and the Central Nervous System. By Henry McIlwain. (Pp. viii + 328; 61 figures, 28 tables. 45*s*.) London: J. & A. Churchill. 1957.

Functional Neuroanatomy. Including an Atlas of the Brain Stem, 3rd ed. revised. By A. R. Buchanan. (Pp. 362; 273 figures, 18 in colour. 56*s*.) London: Henry Kimpton; Philadelphia: Lea & Febiger. 1957.

Pharmakopsychologie und Psychopathologie. By Wolfgang de Boor. (Pp. xi + 291. DM 39.60.) Berlin, Gottingen, Heidelberg: Springer-Verlag. 1956.

The Relationships Between Electroencephalographic and Psychological Data in Normal Adults. (Pp. vii + 152 + 9 figures, 3 tables. Florins 15.-.) Leiden: Universitaire Pers Leiden. 1957.

Eisen, Kupfer und Eiweiss am Beispiel der Leberkrankheiten. By J. Lange; Foreword by Paul Martini. (Pp. viii + 89; 37 figures. DM 13.50.) Stuttgart: Georg Thieme. 1958.

Morphologie und Physiologie des Nervensystems. By Paul Glees. (Pp. xii + 445; 149 figures. DM 58.-.) Stuttgart: Georg Thieme. 1957.

The Analysis of Fantasy. By W. E. Henry. (Pp. 305. 48*s*.) New York: John Wiley. 1957.

Traitement Chirurgical des Anévrysmes Intracraniens du Système Carotidien: Anévrysmes Supra-Clinoidiens. By G. Allègre and R. Vigouroux. (Pp. 122; 28 figures. Fr. fr. 1,400.-.) Paris: Masson. 1957.

L'Encéphalographie Fractionnée. By Giovanni Ruggiero. (Pp. 510; 288 plates (843 figures). Ff. fr. 13,500.-.) Paris: Masson. 1957.

Les Kystes Epidermoïdes Cranio-Encéphaliques. By J. Lepoire and B. Pertuiset. (Reports presented at the Annual Meeting of the French Neurochirurgical Society.) (Pp. 106; 35 figures.) Paris: Masson. 1957.

Atlas d'Anatomie Stéréotaxique. By J. Talairach, M. David, P. Tournoux, H. Corredor, and T. Kvasina. (Pp. 294; 91 plates, 99 figures. Fr. fr. 9,000.-.) Paris: Masson. 1957.

Handbook of Neurological Examination and Case Recording, revised ed. By D. Denny-Brown. (Pp. viii + 114. 22*s*.) Harvard University Press (London: Oxford University Press). 1957.

A Study of Major Psychoses in an English County, No. 3. By M. Shepherd. (Pp. 159 + 28 histograms. 25*s*.) London: Chapman & Hall. 1957.

Scandinavian Neurosurgical Society

The annual meeting of the Scandinavian Neurosurgical Society will take place in Copenhagen on Friday, August 29, and Saturday, August 30, 1958.

Secretary: Bendt Broager, M.D., Bispebjerg Hospital, Copenhagen NV, Denmark.

International Congress of Psychotherapy

The fourth international congress of psychotherapy will be held from Monday, September 1, till Sunday, September 7, 1958, in Barcelona and is organized by the Sociedad Espanola de Medicina Psicosomatica y Psicoterapia.

Secretary: Catedra de Psiquiatria de la Facultad de Medicina Casanova, 143, Barcelona.

.. *Neurol. Neurosurg. Psychiat.*, 1958, **21**, 159.

CEREBELLAR HYPOPLASIA ASSOCIATED WITH SYSTEMIC DEGENERATION IN EARLY LIFE

BY

R. M. NORMAN and H. URICH

From the Burden Neuropathological Laboratory, Frenchay Hospital, Bristol

Hypoplasia predominantly affecting the lateral lobes of the cerebellum has on several occasions been found associated with marked underdevelopment of the griseum pontis and middle peduncle (Vogt and Astwazaturow, 1912; Brun, 1917, 1918; Brouwer, 1924; Biemond, 1955). Brouwer named this condition " hypoplasia ponto-neocerebellaris " and emphasized the fact that the same neuronal system was affected in this prenatal malformation as in olivo-ponto-cerebellar atrophy. Support was thus given to the theory already put forward by Winkler (1923) that a congenital weakness of the derivatives of the cell bands of Essick (1912) underlay the brain-stem degenerations of olivo-ponto-cerebellar atrophy. The two cases described in this paper take this comparison a stage further. Both are examples of cerebellar hypoplasia occurring in infants who died during the first year of life. Detailed examination of the brain-stem in the first case has revealed a much closer resemblance to olivo-ponto-cerebellar atrophy than has hitherto been suspected. More remarkable, however, is that in both our cases there is evidence of degeneration having taken place in certain other nuclei known to be liable to involvement in the systemic degenerations of later life. A bond has thus been disclosed linking malformation with abiotrophy.

Case 1

Clinical History.—J. L., a boy, died at the age of 5 months. The parents were second cousins. The circumstances of birth and early progress had been normal. At 2 months he was brought to a paediatrician because of the peculiar shape of the head. The mother had kept a close watch on the baby's development because his elder sister, who had died at the age of 2½ years, had been microcephalic and mentally defective. On examination, the sutures and the anterior fontanelle appeared to be closed or almost so. The calvaria was described as tapering towards the vertex and sloping inwards at the temples, the head circumference being 14⅛ in. It was thought that this might be a case of craniosynostosis and he was referred to the Bristol Neurosurgical Unit. The child was seen in the Outpatient Department three weeks later and the head circumference was then 14½ in. The retinal veins were not engorged and there seemed to be no indication for immediate operation. On admission to hospital 10 weeks later, it was confirmed that the fontanelles were closed, although the shape of the head did not conform to any of the recognized types of craniosynostosis. The child lay with the head retracted and the limbs spastic and flexed. Tonsillar herniation was suspected and it was considered to be too dangerous to carry out air studies. Parasagittal linear craniectomies were performed but the cerebral gyri were not flattened and the tension not high. Two hours after having apparently recovered from the operation the infant developed signs of respiratory failure and an emergency suboccipital decompression was carried out. It was then discovered that the cerebellum was markedly hypoplastic. The baby died during the operation.

Post-mortem examination revealed no malformation outside the cranial cavity.

Examination of the Central Nervous System in Case 1

Macroscopic.—The brain weighed 497 g. after fixation, the cerebellum and brain-stem accounting for 20 g. The convolutional pattern of the cerebral hemispheres was normal as were the cranial nerves and the arteries at the base. The third ventricle and the inferior horn of the left lateral ventricle were slightly dilated. The cerebellum only reached to within 3 cm. of the occipital pole. It showed the normal anatomical arrangement of lobules but the whole organ was small and flat, the lateral lobes disproportionately so compared with the vermis and flocculi. The pons was short and the pes pontis conspicuously underdeveloped compared with the tegmentum.

Microscopic.—The cerebellum and brain-stem were serially sectioned, every fortieth section being stained for nerve cells and the adjoining section for myelin. The cerebellar cortex showed no significant lesions as regards Purkinje or granule cells. The external granular layer was of normal depth for this age. The central white matter of the lateral lobes was small in amount, poorly myelinated (Fig. 1), and in Holzer preparations showed marked fibrillary gliosis, especially in the hilum of the dentate nucleus.

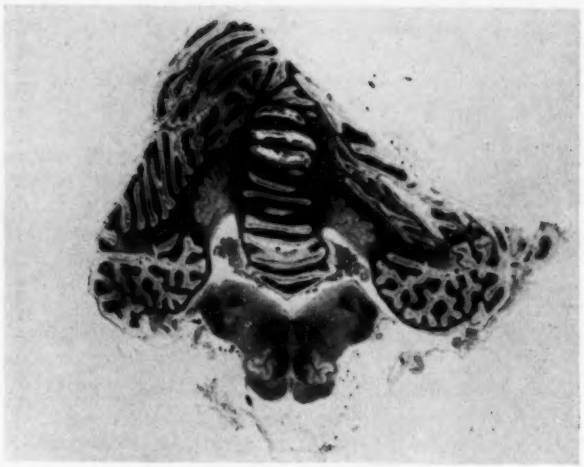

FIG. 1.—Case 1. Cerebellum: poor development of the lateral lobes compared with the vermis and particularly with the flocculi which are of normal size. The dentate nuclei are normally shaped but there is marked poverty of myelinated fibres in the hila.

Heidenhain × 2

Myelination was normal in the vermis and flocculi. The dentate nuclei were severely atrophied, the remaining nerve cells tending to be grouped in small clusters (Fig. 2). These cell nests contained numerous unmyelinated axis cylinders and fewer neuroglial fibrils than the surrounding tissue. It was evident that the dentate nucleus had at one time been normally formed, since in Nissl preparations its crenated outline was clearly marked by a band of astrocytic nuclei joining together the islands of remaining nerve cells. The original shape of the nucleus was also well shown by the myelinated fibres of the amiculum. Nerve cells were more numerous in the dorsal and oral portion of the nucleus which was continuous with the nucleus emboliformis. Here and there a chromatolytic cell with a laterally displaced nucleus was seen but there was no microglial activity. The cells of the nucleus globosus were normal. The nucleus fastigii was represented on each side only by a few nerve cells placed laterally in the roof of the fourth ventricle.

FIG. 2.—Case 1. Dentate nucleus: the majority of the nerve cells have degenerated. The original normal contour of the cell band is indicated by astrocytic nuclei.

Carbol azure × 30

Brain-stem.—The inferior olives were smaller as a whole than in the newborn. In the oral parts of the principal nucleus the dorsal and medial nerve cell band was poorly convoluted and its depth reduced in many places to a single row of irregularly spaced neurones (Fig. 3). There was a well-marked fibrillary gliosis of the hilum and capsule. The arcuate nuclei, together with the external arcuate fibres and the arcuo-floccular fasciculus (stria medullaris), were absent, as was the nucleus conterminalis.

Certain nuclei situated dorso-medially in the medulla were absent or represented by a few cells only, namely, the pararaphales, paramedianus dorsalis, and raphae obscurus. Another group of nuclei normally found in the vicinity of the hypoglossal and prepositai nuclei were similarly affected, namely, the intercalatus, Roller, and interfascicularis. The reticular nuclei were well developed except for the nucleus lateralis medullae which was virtually absent on both sides (Fig. 4). The pontobulbar bodies were also missing. Fibrous neuroglia was increased in the restiform bodies, the nuclear masses in the floor of the fourth ventricle and in the raphe.

The nuclei pontis were extremely poorly represented, especially at caudal levels where only a few small groups or strands of cells were present (Fig. 5). Here the pyramidal tracts were undivided into smaller bundles. At oral levels the griseum pontis was somewhat better developed and thin strands of cells partially surrounded the individual bundles of the descending cortical tracts. The great majority of these cells were small and in marked contrast to the few groups of well-developed neurones. Similar small cells could also be found in the pontine nuclei of a control case of the same age, but here they were relatively scanty. The tegmental extensions of the griseum were absent. The transverse fibres were as yet unmyelinated and in

FIG. 3.—Case 1. Inferior olive: limited convolutional development and neuronal poverty especially in dorsal and lateral parts.
Carbol azure × 20

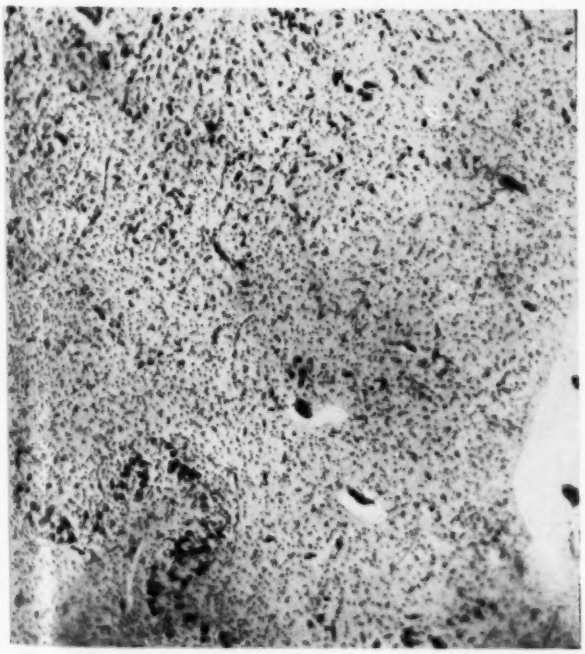

FIG. 4.—Case 1. Medulla: absence of the nucleus lateralis medullae. The dorsal folds of the inferior olive are seen below, the nucleus ambiguus above.
Carbol azure × 30

FIG. 5.—Case 1. Pons at level of superior olives: great reduction in the size of the nuclei pontis. The small pes pontis is almost filled by the pyramidal tracts.
Carbol azure × 6·4

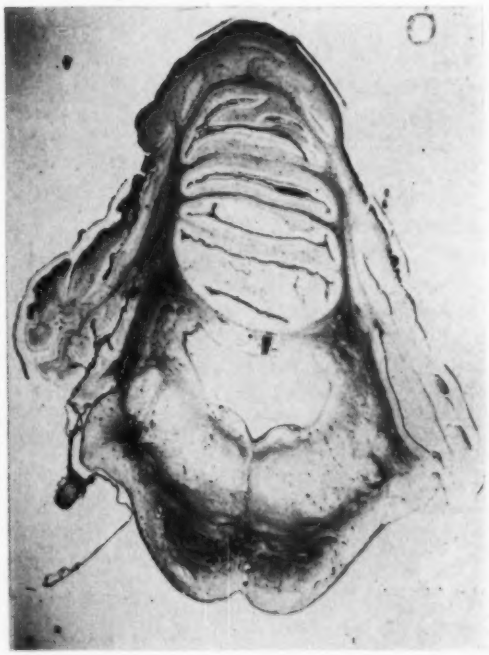

FIG. 6.—Case 1. Pons: fibrous gliosis in the pes pontis.
Holzer × 3·4

FIG. 7.—Case 1. Thalamus: atrophy of the ventro-lateral and antero-ventral nuclei. Preservation of the antero-dorsal and dorso-medial nuclei.

Carbol azure × 10

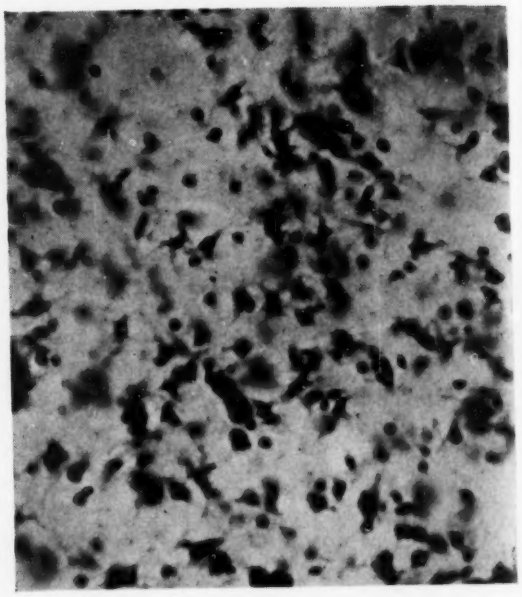

FIG. 8.—Case 1. Microglial proliferation in a degenerated part of the antero-ventral nucleus of the thalamus.

Carbol azure × 240

FIG. 9.—Case 1. Mammillary bodies: severe bilateral loss of nerve cells in the internal nucleus.

Carbol azure × 16

Gros-Bielschowsky preparations they were seen to be very poorly represented. The site of these fibres was densely gliosed (Fig. 6). Fibrillary gliosis of less intensity was present in the pyramidal tracts, griseum pontis, and medial fillet.

Thalamus.—Serial sections of the thalami showed almost complete degeneration of each nucleus ventralis lateralis. Approximately symmetrical lesions were also present in the anterior nucleus but here they were of more recent date. A considerable

number of nerve cells had been lost in the medial and ventral parts of this nucleus, the dorsal accessory nucleus remaining intact (Fig. 7). The pathological areas contained numerous microglial cells, their thickened branches clearly visible in Nissl preparations (Fig. 8). There were no figures of neuronophagia but numerous shrunken, palely staining nerve cells were present in the vicinity of the areas of nerve cell loss.

Hypothalamus.—Severe neuronal degeneration had taken place in the medial nuclei of the mammillary bodies and very few cells remained (Fig. 9). The lateral nucleus was unaffected. There was no astrocytic gliosis but a few hyperplastic microglial cells were present. The blood vessels were normal. The bundle of Vicq d'Azyr was not identified.

Other Parts of the Brain.—Large survey sections of representative parts of the cerebral cortex revealed no significant lesions. The corpus striatum, globus pallidus, and nucleus subthalamicus of each side were also normal. Myelination of the centrum semiovale and the basal ganglia was adequate for a child of this age but there was an abnormal fibrillary gliosis in the internal capsule, the medullary laminae of the globus pallidus, and in the optic tracts. The corpus callosum was normal.

Case 2

Clinical History.—J. A., a girl, was aged 8 months at death. There were three other siblings, all healthy, and the mother had had two miscarriages. The patient was born in the 36th week of pregnancy by Caesarian section on account of placenta praevia. The birth weight was 6 lb. 12 oz. The infant would not suckle and had to be fed by tube. After three months in hospital the weight was 8 lb. and she went home. Her health was precarious and before her terminal illness she had had four admissions to hospital for respiratory or urinary infections. At 18 weeks she was admitted with signs of pneumonia. At this time the circumference of the head was 15½ in. and the anterior fontanelle almost closed. She had made no intellectual progress and appeared to have no appreciation of light or sound. Spastic paresis was noted in the legs. Courses of penicillin and later of terramycin were given with little or no effect and death occurred from bronchopneumonia.

Examination of the Central Nervous System in Case 2

Macroscopic.—The brain after fixation weighed 513 g., the cerebellum and brain-stem accounting for 51 g.

The whole corpus callosum was absent and the cingulate gyri were ill defined. The left calcarine fissure failed to meet the parieto-occipital fissure. Both insulae were partly exposed owing to the poor development of the inferior frontal gyrus. The right superior frontal gyrus and both superior temporal gyri were unduly narrow. The cranial nerves and vessels at the base were normally distributed.

The cerebellum was smaller than normal and about 2 cm. of the basal surface of the occipital lobes remained uncovered by it. The vermis, flocculi, and in particular the lateral lobes, were all hypoplastic and the brain-stem correspondingly small (Fig. 10*a*). The medullary pyramids were absent.

The right cerebral hemisphere was cut in coronal blocks (the left horizontally) and embedded in celloidin. The absence of the whole of the corpus callosum was confirmed and it was noted that no longitudinal callosal bundle was present on either side. The posterior and inferior horns of the lateral ventricles were enlarged owing to the poor development of the central white matter.

Microscopic.—In the cerebral cortex the granular layer of the visuo-sensory area was not divided by a stria of Gennari and contained no stellate cells. Elsewhere no gross abnormality was detected, though there was probably a mild generalized retardation in cortical development. The precentral gyrus contained numerous giant cells of Betz despite the absent pyramidal tracts. The whole of the hemispheric white matter showed a moderate fibrillary gliosis and in general the brain was rather less well myelinated than normal.

The thalamus, putamen, and caudate nucleus were histologically normal. The globus pallidus was unaffected except for its internal segment where the nerve cells were shrunken, some appearing pale, others staining deeply. There was marked fibrillary gliosis in this segment and also in the medullary laminae (Fig. 12) but this was not accompanied by detectable demyelination. The optic tracts were small and gliosed. The anterior commissure was present. Both the *corpora Luysii* were strikingly atrophied, and had lost diffusely about 90% of their nerve cells. The degeneration of the right corpus Luysii appeared to be the more recent since several figures of neuronophagia were seen (Fig. 11) and some of the remaining nerve cells appeared degenerate, with loss of Nissl bodies, swelling of the cytoplasm, and displacement of the nucleus to the margin of the cell. There was a well-marked fibrillary gliosis of the capsule and in the central part of the nucleus (Fig. 12) where the myelinated fibres were reduced in number.

Cerebellum.—There was no appreciable loss of Purkinje or granular cells in the lateral lobes or vermis and the central white matter was well myelinated. The dentate nuclei were small and poorly convoluted (Fig. 10*a*). Many of their nerve cells were shrunken and darkly staining, others were very small and almost devoid of Nissl substance. Here

FIG. 10*a*.—Case 2. (*a*) Relatively small cerebellum and brain-stem. The dentate nucleus is poorly convoluted.
Heidenhain × 1·6

FIG. 10*b*.—A normal control aged 9 months. Same magnification as 10 (*a*).

FIG. 11.—Case 2. Left nucleus subthalamicus: severe neuronal degeneration. Several figures of neuronophagia are present.
Carbol azure × 70

FIG. 12.—Case 2. Fibrillary gliosis of the nucleus subthalamicus and the globus pallidus (mainly the internal segment and medullary laminae).
Holzer × 5

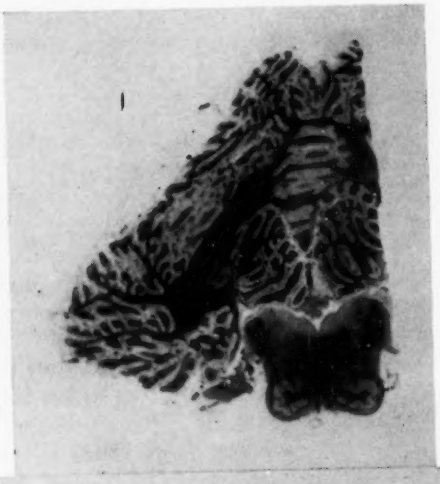

FIG. 10*a*

FIG. 10*b*

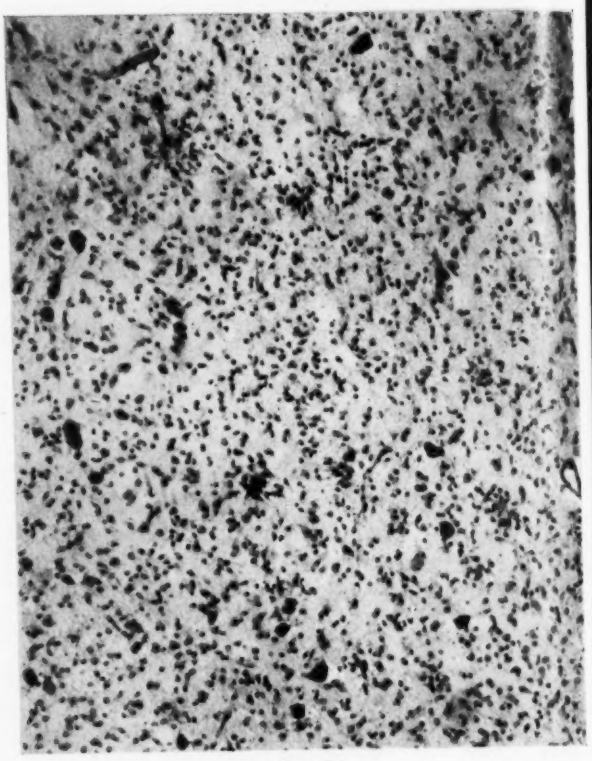

FIG. 11

FIG. 12

and there a patchy loss of nerve cells was obvious. The whole nucleus contained an increased number of astrocytes and in Holzer preparations the hilum showed a mild fibrillary gliosis. The nucleus emboliformis was similarly affected but the globosus and fastigii appeared normal on both sides.

Brain-stem.—The medullary pyramids were absent and the medial fillet poorly developed. The inferior olives showed no loss of nerve cells but caudally the cell bands were poorly convoluted. Serial sections failed to reveal any other abnormality in the nuclei of the brain-stem.

Spinal Cord.—Lateral fissures indicative of absent pyramidal tracts were present bilaterally in the cervical and dorsal segments. In the lumbar region the white matter showed a very dense fibrillary gliosis unassociated with detectable defect of myelination and not extending into the central grey matter.

Discussion

In comparing ponto-neocerebellar hypoplasia with olivo-ponto-cerebellar atrophy Brouwer cited the following structures as predominantly affected in both conditions: the lateral lobes of the cerebellum (Edinger's " neo-cerebellum "), the nuclei pontis and middle peduncle, the arcuate nucleus, and the corpus ponto-bulbare. The inferior olives, a major derivative of the migratory cell bands of Essick, have been found normal or but slightly underdeveloped in several examples of this form of cerebellar hypoplasia. However, in Brun's cases they showed a combination of hypoplasia and neuronal atrophy. Brun also noted a great reduction in the size of the lateral nuclei of the medulla and these also have been found to be degenerated in olivo-ponto-cerebellar atrophy (Winkler, 1923; van Bogaert and Bertrand, 1929; Tans, 1952). The detailed survey of the brain-stem made by Tans in a case of olivo-ponto-cerebellar atrophy has enabled us to elaborate this comparison between the two conditions. In our case, as in Tans', there were also obvious lesions in the perihypoglossal group of nuclei consisting of the nucleus intercalatus, the interfascicularis hypoglossi, and the nucleus of Roller. The nucleus conterminalis, the raphe obscurus, the paramedianus dorsalis, and the nuclei pararaphales were similarly underdeveloped or atrophied. Almost all these nuclei are known to have cerebellar connexions either in man (Uemura, 1917; Olszewski and Baxter, 1954) or in animals (Brodal, 1952). Such a close correspondence in the distribution of lesions cannot be due to chance. Nor is it probable that these brain-stem lesions are secondary to the cerebellar anomaly. Certainly, in olivo-ponto-cerebellar atrophy it is generally held that the pontine, arcuate, and olivary degenerations precede the very variable changes in the cerebellar cortex (Greenfield, 1954). While it is true that unilateral cerebellar hypoplasia may on occasion be associated with contralateral atrophy of olive or pons (Lichtenstein, 1943), this apparently retrograde type of atrophy seems to be the exception rather than the rule and may well indicate that some of the unilateral cases have a different pathogenesis from the bilateral. The brain-stem nuclei in our second case were intact despite the severe cerebellar hypoplasia. We are left with the conviction that Brouwer was justified in seeing the same principle of systemic degeneration in ponto-neocerebellar hypoplasia as in olivo-ponto-cerebellar atrophy. It becomes only a question of degree as to whether the congenital weakness of a neuronal system is so mild as to enable the nerve cells to survive for a number of years or so severe as to lead to atrophy in foetal life or even to a failure of cell division.

If this hypothesis is correct one would expect to find cases in which both prenatal malformations and unequivocal degenerative lesions occurred in the same brain, and in our first case degeneration and not hypoplasia involved the dentate nuclei. This finding is in contrast to previously reported examples of ponto-neocerebellar hypoplasia in which the dentate nucleus has shown a characteristic segmentation into several small islands of nerve cells, an appearance imitating that of the normal 80 mm. embryo (Brun). In the present case, the clumps of nerve cells were evidently residual groups remaining after degeneration and gliosis of a normally convoluted nucleus. The almost complete atrophy of the ventro-lateral thalamic nuclei (in which the bulk of the superior cerebellar peduncles end) is a good example of chain degeneration and has recently been reported in abiotrophies involving the dentate nucleus (Poser, Dewulf, and Van Bogaert, 1957; Urich, Norman, and Lloyd, 1957). A further instance of chain degeneration and one which has no counterpart in diseases of later life was seen in the combined atrophy of mammillary bodies and anterior thalamic nuclei. This lesion is of special interest because of its evidently recent onset, as judged by the local microglial activity.

In the second case the dentate nuclei showed a combination of hypoplasia and atrophy. The most striking degenerative lesions were, however, found in the subthalamic nuclei where the presence of neuronophagia ruled out the possibility that these were lesions dating from the neonatal period. Once again cerebellar hypoplasia is seen in association with degenerative changes appropriate to the abiotrophies of later life (Titeca and van Bogaert,

1946). It is logical to apply the same unifying principle of abiotrophy to the other malformations present in this case. Thus the absence of the pyramidal tracts and of the corpus callosum may be regarded not as the consequence of true agenesis but of early degeneration and resorption. As regards the absent corpus callosum, it is of considerable interest to note that there were no longitudinal callosal bundles. According to Marburg (1949), the absence of these structures, which are aberrant callosal fibres which have failed to cross the midline, is indicative of a destructive process affecting the corpus callosum after its formation. Provided this destruction occurred before the fifth month, the usual associated malformation of the cingulate gyrus might be expected to occur (Becker, 1952). In our case, therefore, it may be suggested that the degeneration and disappearance of the corpus callosum occurred at some period after its initial formation at the third month but before the cingulate convolution was laid down in the fifth month.

There was a strong hint of familial incidence in the first case and certainly the differing times of onset of the various lesions ranging from " pure " malformations to degenerations in active progress suggest the operation of genetic rather than exogenous factors. Clarification of this problem must await the collection of further examples of what at present seems a rare condition, namely, the combination of abiotrophy and prenatal malformation. All that is claimed for the apparently exceptional cases described here is that they form a bridge, albeit a slender one, connecting two categories of pathological process usually regarded as unrelated.

Summary

In two young infants cerebellar hypoplasia has been found associated with neuronal degenerative lesions of a systemic character. The first case was one of ponto-neocerebellar hypoplasia and showed, in addition to the usual developmental anomalies of the griseum pontis, arcuate nuclei, and inferior olives, the involvement of other brain-stem nuclei including the perihypoglossal and certain midline groups in the medulla. This distribution of lesions was remarkably similar in detail to that previously reported in olivo-ponto-cerebellar atrophy. Severe degeneration was present in the dentate nuclei and transneuronal atrophy had occurred in the ventro-lateral nuclei of the thalamus. Another instance of chain degeneration was seen in the combined atrophy of the mammillary bodies and the antero-ventral thalamic nuclei. In the second case cerebellar hypoplasia was accompanied by absence of the corpus callosum and pyramidal tracts. The dentate nuclei showed a combination of mild developmental arrest and atrophy. Severe and recent degeneration was present in the corpora Luysii and this was associated with gliosis and neuronal shrinkage of the internal pallidal segments. These findings give support to the theory first put forward by Brouwer that the same principle of systemic degeneration is to be seen in ponto-neocerebellar hypoplasia as in olivo-ponto-cerebellar atrophy. Some malformations may thus be the early expression of the same abiotrophic process that later reveals itself in the degeneration of certain vulnerable neuronal systems.

We are greatly indebted to Mr. G. L. Alexander and to Dr. A. W. Franklin for the use of their clinical notes and also to Dr. R. J. Sandry and to Dr. J. I. Pugh who performed the post-mortem examinations and kindly made these brains available for examination.

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CLINICAL AND ELECTROENCEPHALOGRAPHIC OBSERVATIONS IN ALZHEIMER'S DISEASE

BY

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Since the beginning of the century a large number of papers have appeared dealing with the pathological and clinical aspects of Alzheimer's disease. Although electroencephalography (E.E.G.) has become a common method of investigation in neurology and psychiatry, very few E.E.G. studies have been reported on histologically proven cases of Alzheimer's disease. In some instances the E.E.G. had been carried out incidentally when the description of the cases was mainly clinical (Stengel, 1943), while in other reports the emphasis was mainly on a therapeutic trial (Sim and Smith, 1955) or on a diagnostic problem (Parr, 1955). Bini (1948), in his monograph on presenile dementias, mentions that the E.E.G. may be normal in some cases or that the alpha rhythm may disappear and be substituted by delta rhythm. The most extensive study appears that of Green, Stevenson, Fonseca, and Wortis (1952) who failed to find any constant difference in the clinical, pneumoencephalographic, and E.E.G. features between five proven cases of Alzheimer's disease and eight of unspecified encephalopathy.

The present study was made in order to assess whether specific E.E.G. features might be recognized in histologically proven cases of Alzheimer's disease and whether E.E.G. investigations might help in the differential diagnosis from other conditions leading to dementia in the presenium. Special consideration was given to the occurrence of seizures and to their relationship to the type and severity of E.E.G. abnormalities.

Material and Methods of Investigation

Senile plaques and Alzheimer's neurofibrillary changes were found in 17 patients who had had previous clinical and E.E.G. examinations. In 12 of these cases the brain was examined after death and in the remaining five satisfactory information was obtained by cerebral biopsy. In all cases the pathological diagnosis was Alzheimer's disease and the specimens were examined in the Department of Neuropathology of the Institute of Psychiatry.

Sixteen cases were studied clinically at the Bethlem Royal Hospital and the Maudsley Hospital, while one case was seen at St. Ebba's Hospital. The clinical features in our material were fairly uniform. The average age of onset was 52 years, the youngest patient being about 31, and the oldest 60. The illness usually began with disturbance of memory and in most cases there was marked apathy. As the disease progressed orientation, speech, written language, and praxis were affected. It was usually at this stage that the clinical diagnosis was formulated. In the final stage a severe dementia and psychomotor restlessness were the dominant features and fits and incontinence were common. Death due to an intercurrent illness occurred, on an average, seven years after the onset of the disease.

The electrical activity of the brain was recorded: (1) In routine resting conditions; (2) after simple stimuli (eye opening or a noise) and during photic stimulation; (3) under the effect of drugs which alter the E.E.G. in a predictable manner in normal subjects.

Either a six- or an eight-channel ink-writing E.E.G. apparatus was used with 20 scalp silver—silver-chloride electrodes. The amplification was of 10 mm. pen deflection for 50 microvolts with a time-constant of 0·3 seconds and a 15% high frequency cut at 75 c./sec. The record lasted 30-40 minutes, including whenever possible three minutes of hyperventilation, and rhythmic photic stimulation. When oral quinalbarbital (gr. 3-4½) was given this additional part of the record lasted about one hour.

E.E.G. Findings

An artefact-free record was difficult to obtain as the patient's cooperation was often poor. However, the use of stick-on electrodes proved of great value. In the frontal region, the potential changes due to eye movement were often troublesome but on occasions we were satisfied that a fair amount of the slow activity picked up from the forehead was of cerebral origin.

Fairly uniform features were seen in all the E.E.G.s and no patient had a normal record. Generalized low or medium amplitude (20-100 microvolts) irregular but often rhythmic 4-7 c./sec. activity formed a fairly constant background with superimposed runs of slower waves. Only occasionally did these show a tendency to bilateral synchrony. Often the slowest components (1½-3 c./sec.)

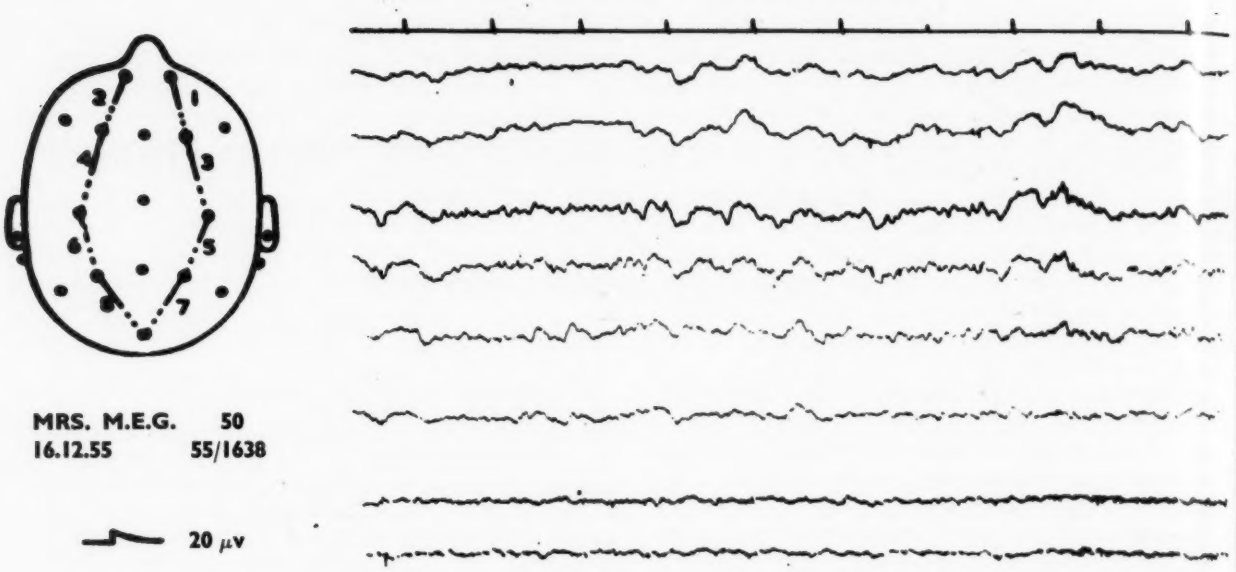

FIG. 1

showed largest amplitude over the anterior part of the head (Fig. 1).

We have classified the severity of the E.E.G. abnormalities in three groups according to the amount of slow activity seen in the first routine resting record of each patient (predominance +++, fair amount ++, small amount +).

In 11 of our cases no alpha rhythms were present in the generalized mixture of slower frequencies. When the alpha rhythms could be recognized these were unstable and scanty, but seemed to be independent of the generalized 4-7 c./sec. activity. Simple stimuli, such as a noise or eye opening, sometimes blocked all activities irrespective of the presence or absence of alpha rhythms.

In Table I some of the E.E.G. features are shown and grouped according to the degree of E.E.G. abnormality in each case. Alpha rhythms were still present in one of the cases with severe E.E.G. abnormality (+++) and in three of those with moderate abnormality (++).

TABLE I
SEVERITY OF E.E.G. ABNORMALITY RELATED TO PRESENCE OR ABSENCE OF CERTAIN E.E.G. FEATURES

	Degree of E.E.G. Abnormality			Totals
	Severe +++	Moderate ++	Mild +	
Alpha present	1	3	2	6
absent	4	7	0	11
Blocking present	2	4	2	8
absent	3	6	0	9
Slow present	5	10	2	17
absent	0	0	0	0
Asymmetries present	2	4	0	6
absent	3	6	2	11
Discharges present	2	4	0	6
absent	3	6	2	11

However, after stimuli the activity was blocked in two cases of severe E.E.G. abnormality and in four of those with a moderate abnormality. Amplitude, or frequency, asymmetries between the activities of the cerebral hemispheres were noticeable in six of the 17 cases.

Transient E.E.G. disturbances in the form of sharp waves, rarely spikes, were seen in six cases. These transient disturbances, lasting 50-100 milliseconds, showed no constant location and sometimes had a tendency to bilateral synchrony (Fig. 2). Only three of these six patients developed seizures, two during the six months preceding death. However, seizures were not uncommon and occurred in 11 of our 17 patients, including two with myoclonic jerks and one with only a single convulsion. One patient had had seizures all her life. The severity of the E.E.G. abnormality did not appear to be related to the presence or absence of seizures by the time the first E.E.G.s were obtained: of the four patients who had had seizures before the first E.E.G. study, one showed a severe E.E.G. abnormality, two a moderate, and one a mild E.E.G. abnormality. The rest had either terminal seizures or no seizures at all.

During overbreathing a slight increase in slow activity was noticed, more marked over the anterior part of the hemispheres. However, only five of our patients were able to hyperventilate for three minutes.

Rhythmic photic stimulation could be adequately performed in six cases and in all of them responses to single flashes could be recognized in the occipital region. In contrast to the apparent disorganization

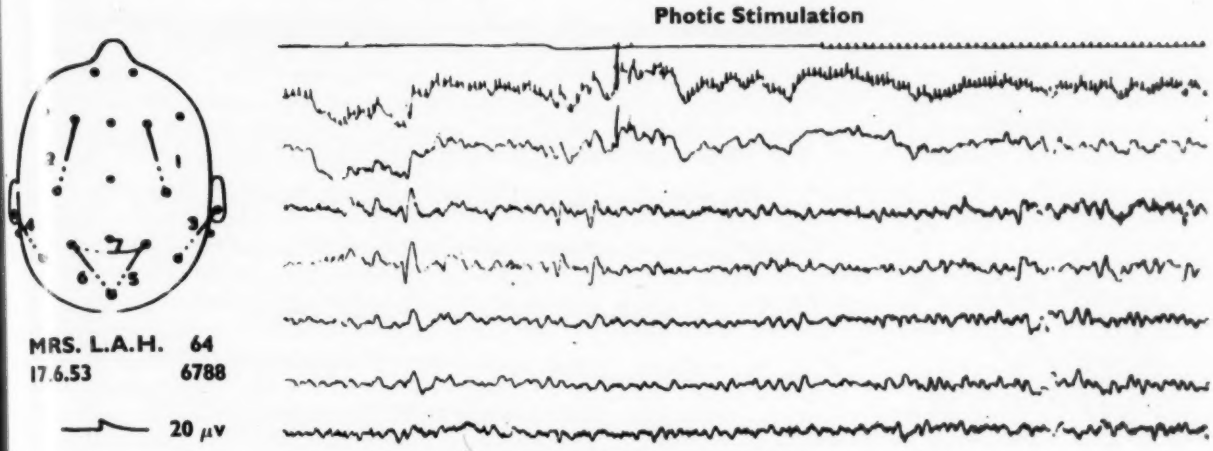

FIG. 2

of background activity, the responses were fairly well preserved and appeared symmetrical over the parieto-occipital regions (Fig. 2). In one of our patients irregular sharp waves, spikes, and large slow waves were elicited by photic stimulation. This patient never had seizures.

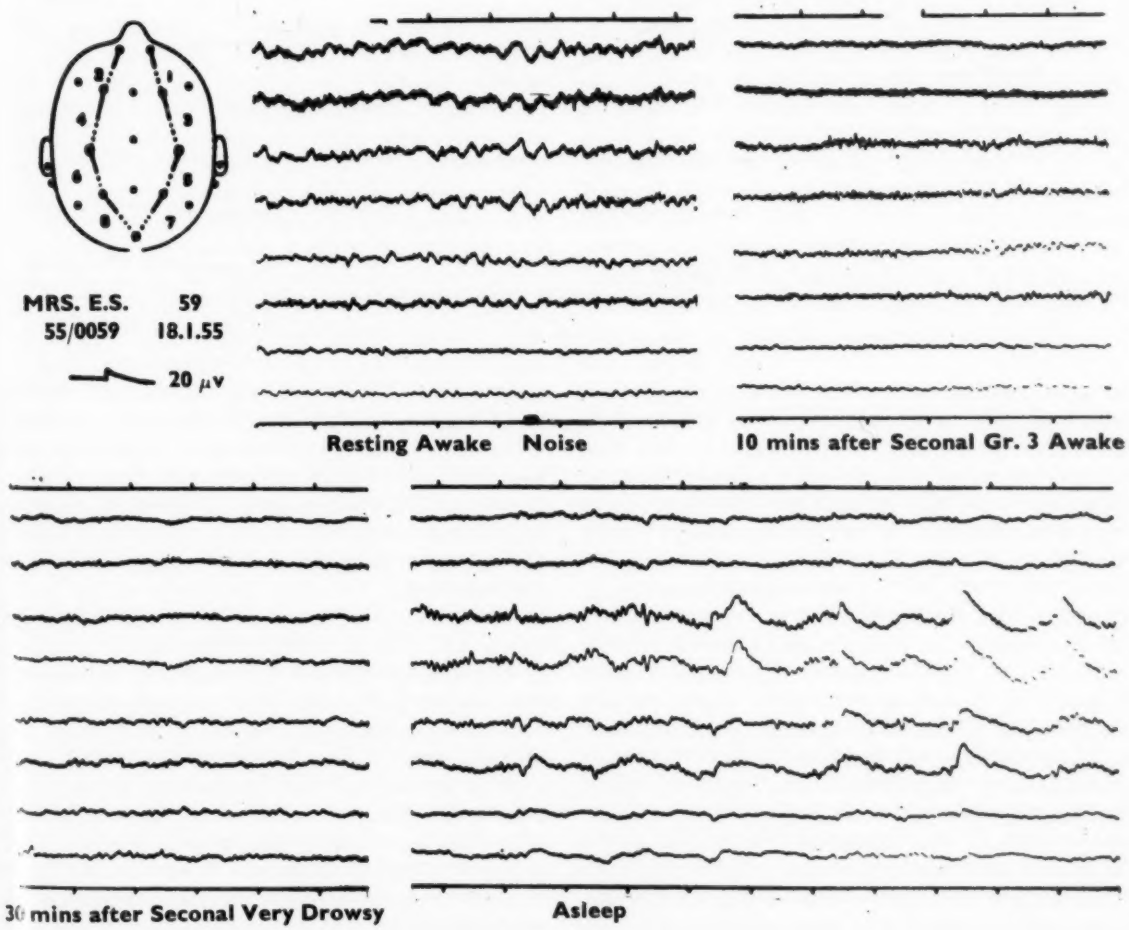

FIG. 3

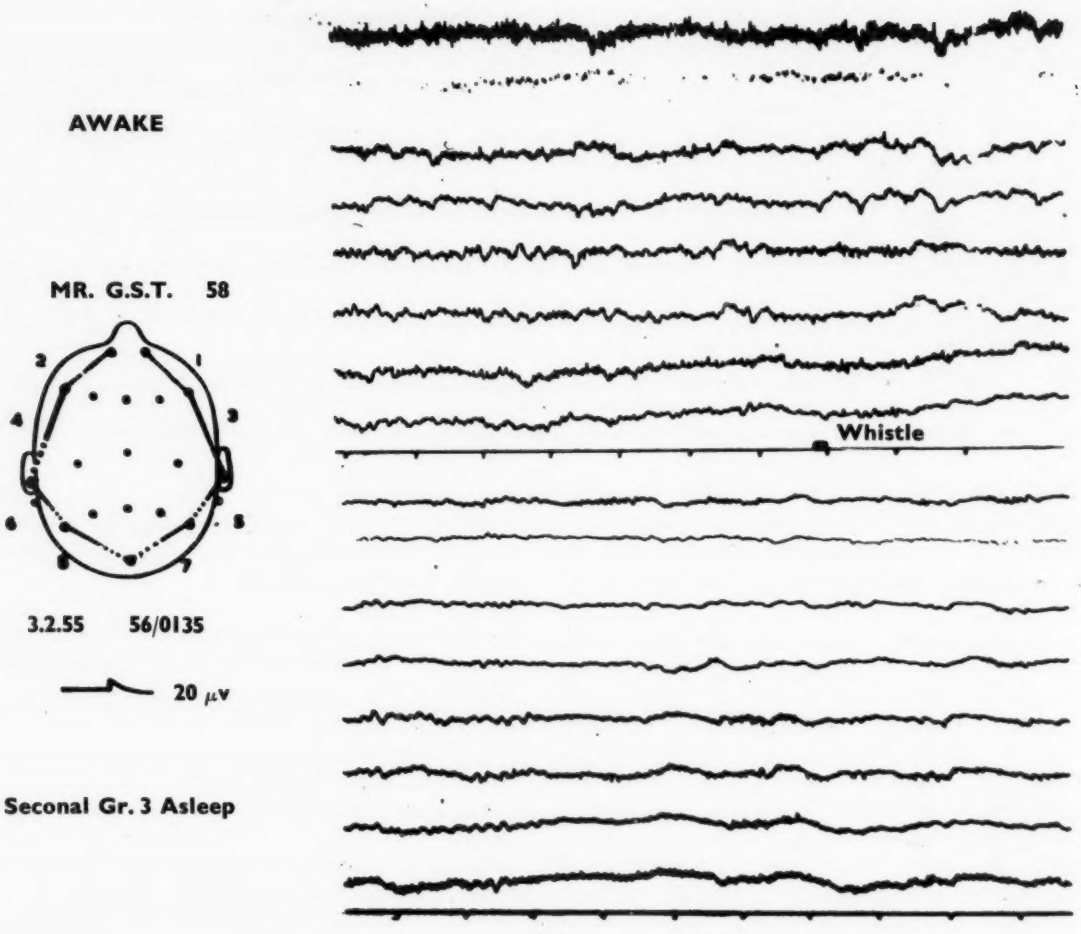

FIG. 4

A relatively quick acting barbiturate (quinalbarbital gr. 3-4½) was administered by mouth to six patients. This additional investigation was performed to assess: (1) The distribution of barbiturate-induced fast activity; (2) the E.E.G. changes during drowsiness and sleep; (3) the effects of sensory stimuli during sleep.

In all cases the barbiturate-induced fast activity was scanty and when recognizable was mainly seen near the vertex. It was usually absent from the prefrontal and fronto-temporal regions. However, the generalized slow activity seen in the routine resting E.E.G. appeared to diminish gradually after the administration of quinalbarbital both during drowsiness and early sleep (Figs. 3 and 4). Sleep spindles were recognized in four of the six cases independently of the degree of abnormality in the resting waking record, but were usually of small amplitude over the anterior frontal regions (Fig. 3). Large repetitive slow waves were seen during deeper sleep with a tendency to bilateral synchrony. Sensory stimuli (noises, calling the patient by name, touching the patient's hand) appeared to evoke K complexes less easily than in other patients of similar age group in a comparable state of sleep. Again no constant asymmetries were noticed during sleep between the activities of the two hemispheres even when some asymmetry was present during the waking state.

Discussion

The present contribution based on 17 histologically proven cases of Alzheimer's disease suggests that the E.E.G. abnormality found in all cases is of an unusual type. The slow activity in the resting records did not appear to be related to the patient's drowsiness as it was increased by overbreathing and on the contrary diminished during induced drowsiness and early sleep. Moreover, the poverty of alpha rhythms with a diffuse predominance of slower activities, the sequence of changes from the resting state to overbreathing, to drowsiness and

barbiturate-induced sleep, and the poor fast activity response to barbiturate are uncommon in other conditions.

The slow activity in the waking state was generalized, often irregular, though sometimes rhythmic. It was not of the sinusoidal 2-3 c./sec. kind seen, for example, during overbreathing in young subjects, during hypoglycaemia, during recovery after a major seizure, or as a *phénomène a distance* in circumscribed cerebral lesions. The amplitude of the slow activity in most records during the waking state was between 50 and 150 microvolts. The uniform distribution of the slow activity over both hemispheres with such an amplitude contrasts with the rather low amplitude slow activity with patchy distribution seen in cerebrovascular disease. In tumours of the corpus callosum the runs of slow activity may appear similar to those of our cases, but usually the alpha rhythms are well preserved in the background. In unilateral intracranial tumours the irregular slow activity is usually fairly well localized.

The poor fast activity response to barbiturates is not related to the age group of the patients tested (sixth decade). In fact, in a group of elderly psychiatric patients, Pampiglione and Post (1955) found that even after 80 years of age the barbiturate-induced fast activity could appear with features closely similar to those found in younger subjects. The scanty fast activity seen in our patients was recorded mainly from electrodes in the para-central region, that is to say, that most other areas of the brain did not modify their activity in a normal way in response to the drug (Pampiglione, 1952, 1954). It is tentatively suggested that the poor barbiturate-induced response in the E.E.G. of our patients might be in keeping with the diffuse cortical lesion characteristic of Alzheimer's disease.

It was considered unprofitable to relate the E.E.G. features to the degree of plaque formation because of the variable time interval between the date at which the E.E.G. studies were performed and the time of death. For the same reason the degree of cerebral atrophy and the main distribution of the plaques were not compared with the E.E.G. findings. It is, in fact, probable that the histological picture varies gradually in each case over months and years and the post-mortem findings may not be a faithful picture of the extent of the pathological process at the time of the E.E.G. studies.

Although cerebral biopsy can provide information about histological changes in the brain soon after the E.E.G. studies, the smallness and localized nature of the specimen permits no generalization about the distribution and severity of the lesions.

A number of patients suffering from dementia in the presenium have been studied at the Bethlem Royal and the Maudsley Hospitals. From this material, in addition to our 17 proven cases, we have collected 19 other cases of the Alzheimer-Pick syndrome in which satisfactory E.E.G. studies were performed. In 15 of these air encephalograms showed some degree of cerebral atrophy. The clinical and E.E.G. features were similar to those of our histologically proven cases (see preliminary communication Letemendia and Pampiglione, 1956) and to three proven cases examined by Dr. D. W. Liddell (personal communication, 1956). In spite of such a similarity we have limited this paper to the histologically verified cases for the following reasons.

In the literature most of the authors do not specify whether their cases were diagnosed only on clinical data and/or pneumoencephalography, or whether histological verification was obtained. In the last few years only Green *et al.* (1952), Sim and Smith (1955), and Parr (1955) state that a cerebral biopsy was obtained from those of their patients who had E.E.G. studies.

A variety of E.E.G. features have been described in patients suffering from so-called " presenile atrophy ", " *demence atrophique* ", and " presenile dementia " (Mengoli, 1951; Mundy-Castle, Hurst, Beerstecher, and Prinsloo, 1954; Hill, 1948, 1955; Rossini, Reggiani, and Zanocco, 1955). These terms are broad and vague, cannot be taken to define any clinico-pathological entity, and probably cover a variety of pathological conditions. The inclusion of unverified cases in the literature of the E.E.G. changes in Alzheimer's disease may account for this lack of uniformity.

In the 12 brains in our series examined at necropsy the atrophy was usually diffuse. Macroscopic cerebrovascular lesions were seen only in one case according to Dr. J. Brierley who examined the brains of our group of patients. In another case an asymptomatic meningioma, one inch in diameter, was found in the left posterior fossa. The E.E.G.s in these two cases were not substantially different from those of the others, apart from showing a moderate asymmetry between the activities of the two cerebral hemispheres.

The E.E.G. abnormality in the individual case was unrelated to the severity of the dementia or to any particular manifestation including aphasic, agnostic, or apractic disturbances. In our series the incidence of fits was rather higher than that reported in the literature. Rothschild (1934) found seizures in 16 out of 53 cases in his review of the literature, Stengel (1953) noted four patients with fits in his series of nine cases, and Sjögren, Sjögren, and Lindgren (1952) four out of 18. In spite of the high

incidence of seizures in our group of cases, the type and severity of the E.E.G. abnormalities did not appear to be related to the occurrence (or to the absence) of fits.

It might be possible to study longitudinally by serial E.E.G. a restricted number of patients in order to assess more precisely whether any fluctuations occur in the E.E.G. pattern of an individual patient over a period of years. In some of our cases up to four E.E.G.s were taken over a one-year period without any significant change in the pattern. However, we were unable to obtain systematic serial routine waking E.E.G.s largely because of the patients' poor cooperation. We did not think it profitable to perform serial E.E.G. studies during barbiturate-induced sleep, as the abnormalities in our series of cases appeared to diminish during sleep, even when gross during the waking state.

We may conclude that the E.E.G. abnormalities seen in our group of proven cases of Alzheimer's disease are unusual in other conditions. Careful study of E.E.G.s may help the clinician in the differential diagnosis of presenile dementias, particularly when the possibility either of cerebrovascular disease or of an intracranial tumour has to be considered.

Summary

Clinical and electroencephalographic studies were made in 17 cases of Alzheimer's disease, later verified histologically (in 12 from necropsy material and in five from cerebral biopsy).

The clinical and E.E.G. features are discussed, including the E.E.G. changes during photic stimulation, after administration of barbiturates, and during sleep.

The common E.E.G. findings were: Absent or scanty alpha rhythms; generalized 2-7 c./sec. activity poorly affected by sensory stimuli, slightly increased by overbreathing but clearly diminished during drowsiness; well-preserved responses to photic stimulation; and poor fast activity response to barbiturates. Sleep spindles were recognizable though often of low amplitude; K-complexes were only infrequently evoked by sensory stimuli.

The E.E.G. abnormalities were fairly uniform in all cases without constant relationship to the duration and severity of the clinical picture, the presence or absence of fits, or the patient's age.

It appears that careful E.E.G. investigations may help the clinician in the differential diagnosis of patients presenting with dementia in the presenium.

We are indebted to Professor A. Meyer and Dr. J. Brierley for post-mortem and histological studies; to Mr. P. Schurr for the cerebral biopsies; to the late Dr. Sands and to Dr. Irwin (St. Ebba's Hospital) for access to the notes and E.E.G.s of one patient; to Professor Stengel and Dr. D. Hill for their advice and encouragement; and to Sir Charles Symonds, Dr. G. Russell, and Dr. J. Marshall for their suggestions and criticisms.

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INVESTIGATIONS OF E.E.G. FINDINGS IN PRESENILE DEMENTIA

BY

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The diagnosis of presenile dementia is used in its widest sense. Clinically, it is impossible to distinguish between the various neuropathological subgroups that make up this group of dementias. The exact diagnosis is only ascertained at death, although biopsies may be diagnostically useful.

There appears to be considerable doubt about the E.E.G. findings in this group of patients. Hill (1948), in 16 cases of presenile cortical atrophy, found an abnormal E.E.G. in eight and a severely abnormal E.E.G. in four. This abnormality appears to have been local delta and slowed alpha at 6 to 8 c./sec. Green, Stevenson, Fonseca, and Wortis (1952) divided a series of presenile dementias into cases of Alzheimer's disease and those not of Alzheimer's disease on the basis of cortical biopsies. They concluded that there was no specific E.E.G. pattern in Alzheimer's disease. In five out of seven of their cases, slowing of the alpha rhythm and very slow irregular delta waves were present. The delta wave activity was diffuse but most marked in the temporal and posterior parietal regions, often on one side more than the other. On the other hand, eight cases of presenile dementia which were not Alzheimer's disease showed slowing of the alpha rhythm associated with focal abnormalities, consisting of voltage depressions or paroxysmal activity, not confined to any particular area. Mundy-Castle, Hurst, Beerstecher, and Prinsloo (1954) found only one abnormal E.E.G. in a series of 10 presenile dementias. However, in his senile psychotic group diffuse delta and theta rhythms were observed and occurred most often in the most severely demented cases.

Material and Method

In view of this uncertainty, it was determined to investigate the E.E.G. findings of the patients suffering from presenile dementia in this hospital. All cases of organic dementia below an arbitrary age of 70 years were selected for investigation, and it was then found that 11 patients fell into this group. The diagnosis was made on clinical grounds and the atrophy was confirmed by air encephalography. In addition, three of the patients have since died and have been investigated pathologically, confirming the clinical diagnosis of Alzheimer's disease, From the clinical point of view these cases showed an insidiously progressive course of deterioration, involving the social, intellectual, and emotional components of the personality. Eventually they arrived at a state of severe dementia in which dysphasic and dyspraxic symptoms dominated. A number of these patients at some time or another had attacks of momentary loss of consciousness. These attacks, however, were very infrequent. In all these cases the Wassermann reaction was negative and there was no gross cardiovascular disease. It is important to stress that the onset and progress of the illness was smoothly continuous and in no way episodic like a further group of dementias associated with vascular disease. Similarly, such nosological entities as Huntington's chorea were excluded.

This group of cases of presenile dementia consisted of two men and nine women with an average age of 60 years, ranging from 51 to 66 years. In most cases the degree of dementia was so severe that they were incapable of being tested by routine psychological tests. The E.E.G.s were taken with an Ediswan six-channel machine.

Results

The findings in all cases were similar. The records showed a generalized basic rhythm of diffuse medium amplitude theta or slow alpha activity at 6 to 8 c./sec. Superimposed on this basic activity, paroxysmal bursts of synchronous high-amplitude delta waves occurred. These bursts had a tendency to repeat themselves rhythmically and were of greatest amplitude in the frontal and temporal regions (Figs. 1 and 2). For long periods this paroxysmal activity was absent and during these times the basic activity changed. It now showed a polyrhythmic pattern composed of medium-voltage mixed delta and theta wave activity. The background activities, as well as the paroxysmal bursts, were temporarily inhibited when the patient's attention was aroused by visual or auditory stimuli. At these

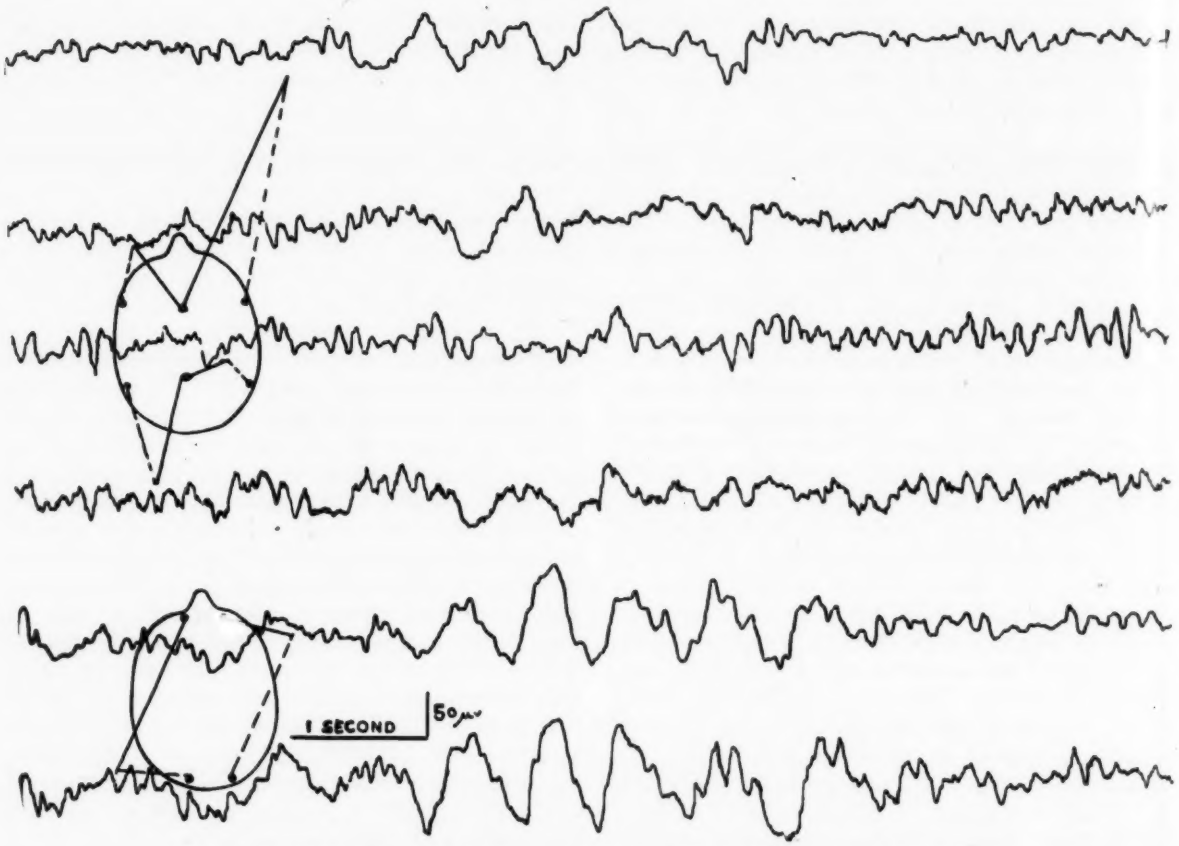

FIG. 1.—Repetitive delta bursts occurring on a background of mixed theta and slow alpha waves.

times an alpha rhythm appeared in most cases. However, even if the eyes remained open, the basic slow activity soon replaced the alpha wave activity. The appearance of the alpha wave activity also occurred spontaneously, breaking through the basic pattern of slower activity (Fig. 3). It was felt that this emergence of alpha activity was possibly related to visceral afferent impulses arriving at the cortex and temporarily holding the patient's attention, as no obvious external stimuli were discernible. When these patients were subjected to photic stimulation the electrical cortical activity followed at the same frequency.

This type of record bore a resemblance to light sleep with spontaneous K complexes, with, however, no sleep spindles. However, when sleep was induced with "pentothal" or "seconal" the record flattened, the paroxysmal delta activity was abolished, and later high-amplitude, irregular, very slow delta waves dominated, with 10 c./sec. spindles frontally. At no time could K complexes be elicited. The fast activity reduced by barbiturates was absent, as Pampiglione (1952) showed in cases of cortical atrophy.

If presenile dementia is but a form of early ageing rather than a specific pathological process, then such a type of record should be common among the senile population of this hospital. Again, it might be argued that the traces are not specific and were related only to apathy and dementia *per se*. For this purpose, 100 patients, whose ages ranged from 70 to 85 years, were subjected to an E.E.G. investigation. These patients often showed a considerable degree of organic deterioration, mostly due to cerebral vascular disease. In this group of 100 senile patients, only seven patients (two men and five women) showed a trace similar to that in the group of patients with Alzheimer's disease. Clinical examination of these patients showed a profound degree of dementia of many years' duration, starting before the age of 70 years. They were thought to be closely related cases, if not actual cases, of Alzheimer's disease of relatively late onset. In fact, one patient has since died and necropsy findings were pathologically indistinguishable from those of Alzheimer's disease. Of clinical interest, in passing, it would appear that the earlier the onset of symptoms in presenile dementia, the more rapid is the

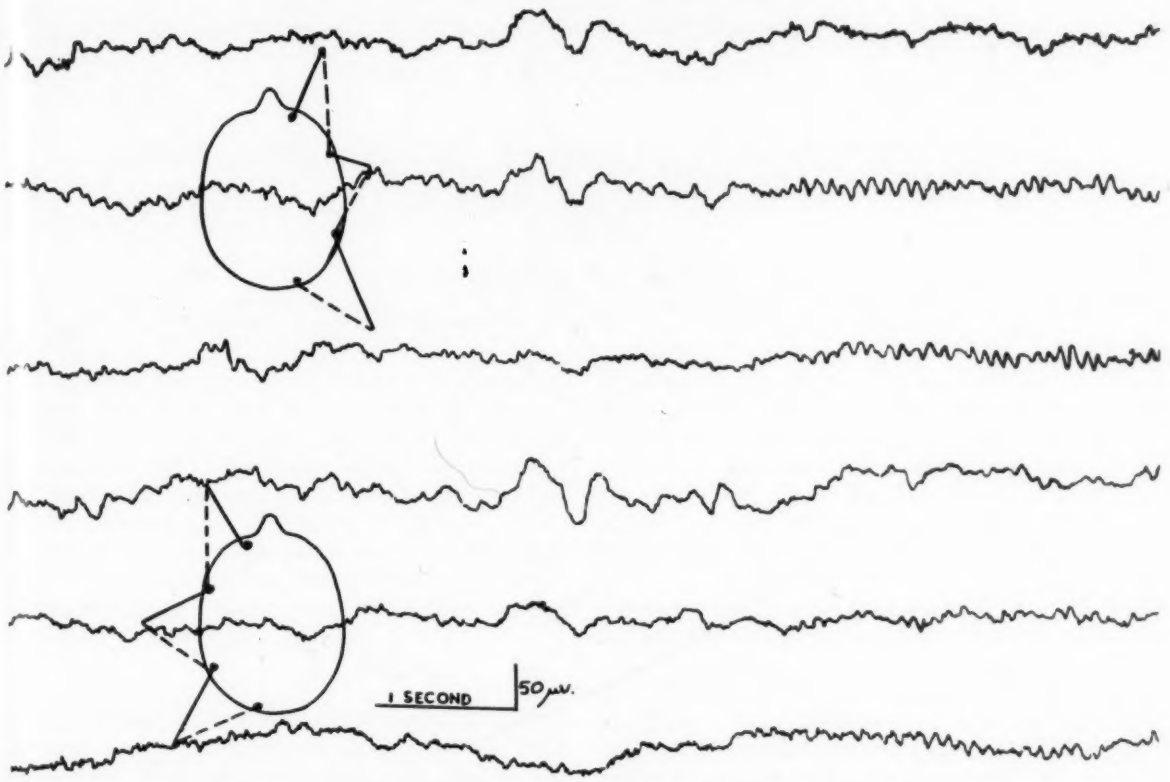

FIG. 2.—Spontaneous delta paroxysm occurring on a slow alpha 6 to 8 c./sec. background.

clinical course of the illness, and conversely, those patients whose symptoms develop later in life run a more slowly progressive course.

It is now generally accepted that it is impossible to distinguish pathologically between Alzheimer's disease and senile dementia, as both are characterized by neurofibrillary tangles and senile plaques. Electroencephalographically, these two groups of presenile and senile dementia also appear to be similar. The E.E.G. findings then suggest that the pathology is specific and in no way connected with the process of normal ageing or simply to dementia, as equally severe cases of dementia due to vascular disease did not show this type of tracing.

These types of record appear to be related to the lowered awareness which these patients show clinically. Under the influence of afferent stimuli, such as photic stimulation, the cortex is temporarily able to behave in an electrically normal manner, in spite of the presence of gross cortical atrophy. This suggests that there are sufficient cortical cells remaining in these patients to respond in an electrically normal manner under stimulating conditions. However, in the absence of this added specific stimulation, such normal activity is not recorded, except temporarily when patients first open their eyes and this in itself is a strong afferent stimulation. Instead, a pattern of rhythmically occurring delta waves superimposed on a slow background of theta wave activity was obtained. The response to photic stimulation suggests that the origin of the abnormal E.E.G. is not cortical and, therefore, appears to arise from deeper structures. By analogy, is this so, as the delta bursts are bilaterally synchronous and arise frontally, for a similar localization is seen in spike-and-wave discharge and in normal K complexes. In these conditions the origin of these waves is thought to be from deep midline nuclei.

In view of the severe cortical atrophy, this response might be considered in the nature of a release of deep midline nuclei from cortical control. This suggestion is further strengthened by the resemblance of these records to those obtained in sleep, in which cortical function is inhibited. Clinically, this paroxysmal activity may well be related to the occasional lapses of consciousness that these patients sometimes show.

The findings in our series suggest that in presenile dementia the E.E.G. is grossly disturbed. The traces are probably similar to those of Hill (1948) and Green *et al.* (1952). While the abnormality is not specific for an exact pathological diagnosis, it is

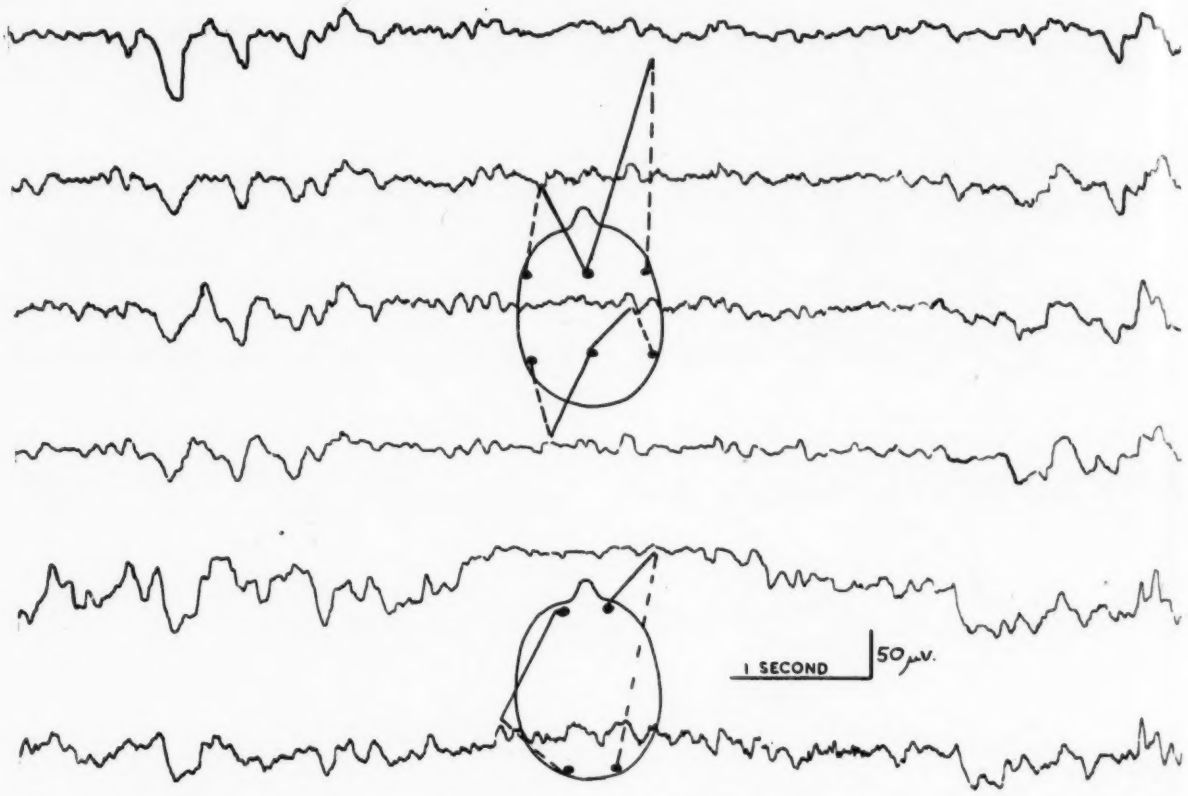

FIG. 3.—Mixed delta and theta activity with a larval anterior delta burst, showing sudden spontaneous appearance of normal alpha wave activity.

sufficiently recognizable and striking to suggest at once the diagnosis of severe dementia due to cortical atrophy of Alzheimer type.

Summary

Electroencephalographic examinations were carried out on 18 cases of severe dementia, consisting of 11 cases occurring during the presenile period and seven cases during the senile period, and all showing classical symptoms of Alzheimer's disease.

The records were grossly abnormal and were sufficiently unusual to be a useful aid in the diagnosis of dementia due to cortical atrophy of the Alzheimer type.

The sex ratio of these 18 patients is four male to 14 female patients but the number is too small to be definite about a sex difference in Alzheimer's disease.

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THE CENTRIFUGAL PATHWAY FOR MICTURITION WITHIN THE SPINAL CORD

BY

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In previous papers we have described the location in man of the spinal pathways subserving sensation from the lower bowel and the motor aspects of defaecation (Nathan and Smith, 1953), and the spinal pathways subserving sensation from the bladder and urethra (Nathan and Smith, 1951; Nathan, 1952). It remains now to show the location in the spinal cord of the pathways used in the conscious control of micturition and those used for the coordination of bladder functioning.

Historical

The location of these fibres in the spinal cord both of man and other animals has been relatively neglected. Most observers who have studied the functional anatomy of micturition have considered the peripheral nerves of the bladder, the effects on the bladder of total transverse lesions of the spinal cord, and they have studied those centres in the brain, stimulation or lesions of which affect the tone and other reflex activity of the bladder. The first worker to investigate the location of the tracts subserving micturition was Budge; he worked on the subject in 1842 and published his results and conclusions in 1864. He obtained bladder contractions in the dog, cat, and rabbit by electrically stimulating the cerebral peduncles, the inferior cerebellar peduncles, and the region between these peduncles and the calamus scriptorius. In one animal, he cut through the posterior columns, and obtained contraction of the bladder, rectum, and Fallopian tubes from stimulating the rest of the spinal cord; he concluded that the descending pathway must lie in the anterior half of the cord. Mosso and Pellacani (1882) criticized Budge's work, as they found that his mode of stimulating the cord was bound to cause much spread of the current. They induced bladder contractions in the dog by painfully compressing the paws. To determine the spinal course of the tract conveying impulses giving rise to these contractions, they carried out various partial sections of the cord. Their conclusions were: "Dans les cordons antérieures de la moelle et dans la partie antérieure des cordons latéraux, il ne passe pas de fibres motrices de la vessie." Stewart (1899), who worked on the cat, found that "bladder contractions can be produced by stimulating the cord at any point"; and he also found that "stimulation of the cord often causes an already contracted bladder to relax". He came to the conclusion that, "Above the vesical centre . . . impulses pass down the cord in the posterior half of the lateral columns only. . . Below the level of the centre the impulses were shown to pass in the lateral columns." He placed the vesical centre in the lumbar cord. Spiegel and MacPherson (1925) found that in the cat complete section of the anterior and posterior columns failed to interrupt the pathway; and they concluded, by increasing the area of cord sectioned, that the fibres subserving bladder contraction must run in the lateral columns. Further work on this subject in the cat led Hunsicker and Spiegel (1933) to conclude that the descending corticofugal tracts to the bladder are conveyed both by pyramidal and extrapyramidal pathways.

In our opinion, the best work on the location of the tracts subserving micturition is that of Barrington (1933). He summed up the results of his work, in 1948, as follows:

> "In the cat, micturition is affected in the same way as by a spinal transection if the periphery of the dorsal half of the lateral column is destroyed on both sides in the upper lumbar region, but it remains unaffected if symmetrical lesions are made in other parts of the cord at this level. It is probable that the periphery of the dorsal half of the lateral columns is the part of the cord containing the tracts used in micturition in the segments above the lumbar region."

He also showed (1933) that:

> "The centrifugal and the centripetal paths of micturition undergo extensive crossing in the segments from which the pelvic nerves arise and possibly in the segment next in front of these."

Wang and Ranson (1939) caused bladder contractions in the cat by stimulating the hypothalamus, and sought for the descending pathway conveying impulses giving rise to the bladder contractions by making various lesions; their most caudal lesion was

at the first and second cervical segments. They came to the conclusion that the descending tract mediating impulses to the bladder lies at this level in the antero-lateral column. Levin and Langworthy (1937) showed that lesions in the cat's tegmentum, not involving the cerebral peduncles and thus sparing the cortico-spinal tracts, cause increased responses of the detrusor musculature to stretch and to " peripheral stimulation in the sensory domain of the sacral and coccygeal segments ", changes which eventually lead to a decreased vesical capacity. Later, Langworthy (1940) showed that electrical stimulation of the cortico-spinal tract causes bladder contraction. Thus, Langworthy has brought forward evidence that there are pathways both within and without the cortico-spinal tract in the cat which are concerned with bladder functioning. Tower (1940), however, found in the monkey that dividing the cortico-spinal tract bilaterally caused " no urinary or faecal incontinence or retention ".

Thus, the evidence for the location of the descending pathways to the bladder centre in the cat is fairly consistent: the pathways lie in the lateral column of the cord. It is not agreed whether the fibres lie in the dorsal or ventral parts of these columns. The evidence indicates that some of the fibres run with the cortico-spinal tract and some run outside this tract.

Before the turn of this century, no mention of the location of these tracts within the human spinal cord had been made. In 1900, von Czyhlarz and Marburg wrote that the tracts connecting the cerebrum with the sacral cord " seem to run in the neighbourhood of the pyramids. But in order to get permanent disorder of bladder function, it seems that both pyramids must be damaged, and damaged to a large extent ". Nineteen years later, Müller (1918) still had to state:

> " We have no information concerning the paths in the spinal cord by which the bladder centres receive their stimulation or inhibition from the brain. We do not know in what part of a section of the spinal cord we should seek them. We have no proof that the impulses to the smooth muscles of the bladder make use of the centrifugal pyramidal tract."

And in 1926, Dennig wrote that doubt might be cast on the hypothesis that the motor tract in man lies in a similar position to that which it occupies in animals. He wrote that lesions of the spinal cord giving rise to severe disorders of micturition may not involve the lateral cortico-spinal tracts, and that lesions of the lateral cortico-spinal tract may cause no disorders of micturition. He pointed out, however, that it is hazardous to draw conclusions from clinical conditions, for the upper motor neurone lesion might not involve the nerve supply to all muscle groups.

The first workers to present any experimental work on man designed to show the location of these tracts were Foerster and Gagel (1932). They stated in their text that bilateral cordotomy " repeatedly " gave rise to retention of urine, although the retention was always temporary. They drew the conclusion that :

> " the descending tract in the spinal cord subserving bladder innervation runs partly in the antero-lateral column. This conclusion has to be drawn from the retention of urine that initially follows the operation. But vesical tracts must also run in other columns, for even after the most complete bilateral antero-lateral cordotomies, the bladder behaviour shows complete recovery."

It must be pointed out, however, that this part of their study of the effects of cordotomy is inadequate, and that the very short case histories appended to their text do not always support the conclusions they drew. In their paper there are 17 cases of bilateral cordotomy; in two of these cases the state of micturition of the bladder is not mentioned. In a further six cases the evidence presented does not give support to the statements they made. In one case, due to collapse of the vertebrae, there was retention of urine before the cordotomy; and in another case the collapse of the vertebrae occurred one week after the cordotomy, making further observations on the effects of cordotomy impossible; another patient died one week after the operation. Two patients died three months and eight months respectively after the cordotomy, from cystopyelitis —a condition which usually follows paralysis of the bladder. A further patient two months after the cordotomy still had retention of urine.

Langworthy and Lewis (1935) concluded from two cases of disseminated sclerosis which they studied in detail (unfortunately without obtaining post-mortem evidence), that their patients' urgency and frequency of micturition was related to " damage to the lateral columns of the spinal cord in the neighbourhood of the cortico-spinal tracts ". In 1940, Langworthy, Kolb, and Lewis stated that the pathway " controlling tone in the vesical muscle . . . probably lies in the lateral columns close to the cortico-spinal tracts ". Presumably, they drew this conclusion from the two cases already mentioned and the evidence from experimental work on animals.

Wruck (1943) stated that extensive antero-lateral cordotomies do not cause bladder disturbance; and from this he concluded that the centrifugal tracts to the bladder probably do not lie between the antero-lateral and postero-lateral columns. No evidence was given in his paper apart from the bald state-

m nt; it seems that his views were based on Foerster's ex perience, already quoted.

Thus we see that in man there is no adequate ev dence apart from that provided by Foerster and G gel; and this is most unsatisfactory. Langworthy *et al.* wrote in 1940:

> " Pathological studies in man are needed to delimit more clearly the pathways controlling micturition. It will be of interest to observe whether these studies will confirm the anatomical localization suggested by animal experimentation."

Such studies in man are presented here.

Effects on Bladder Functioning of Dividing the Spinal Cord

When all the spinal tracts subserving micturition have been divided, the resulting disturbance of function resembles, though it is not identical with, that which follows when the spinal cord has been totally divided. Before considering the present series of cases, the functioning of the bladder when the cord is divided will be briefly reviewed. It is immaterial at what level such a transection occurs provided it divides the sacral centre from those centres above the medulla oblongata that play a part in the control and coordination of micturition.

Transection of the cord interrupts the sensation of pain from the bladder and the normal sensation underlying the desire to micturate, and the control of micturition permanently; but the behaviour of the automatic bladder, cut off from impulses arising above the spinal cord, is a changing one. This changing course of reflex and postural activity is usually considered to pass through three stages; these will now be briefly considered.

Most writers on this subject write of the state of the visceral musculature of the bladder as being regulated by the same factors that regulate the state of the somatic musculature. This is an assumption. Whether this assumption is justified will not be considered here, as it does not influence the observed behaviour of the bladder.

The bladder, like all muscle, has tone or posture. Posture was designated by Sherrington (1915) as:

> " that property of the bladder by virtue of which it solves the problem of acting as a reservoir for quantities of fluid of very varying volume from one occasion to another without allowing the intravesical pressure to attain the reflex stimulus threshold height with one particular fluid quantity only."

This postural activity is under the constant influence of centres situated cranial to the spinal cord.

When the spinal cord is suddenly divided, the bladder is then, according to most observers, in a state of flaccidity or atonicity. The cystometrograph shows the flat type of curve typical of low pressure. In fact, the viscus certainly possesses some intrinsic tone, for it is not completely flaccid even when all the nerves between it and the sacral centres have been divided. Further, some recent workers consider that the type of curve seen in the early stage after division of the cord results from stretching the musculature of a bladder in which the micturition reflex is absent. At this time, there is no vesical reflex activity; there are no detrusor contractions and no micturition reflex, and these cannot be induced by the injection of carbaminoyl choline. The sphincters are tightly shut. Just as with the somatic musculature, in which the stage of flaccidity with spinal shock eventually gives way to a stage of increased reflex activity characteristic of the spinal cord functioning independently of the centres cranial to the medulla oblongata, so in the bladder there follows a stage of increased reflex activity; reflexes are increased in the sense that they fire off with lesser stimuli and that the resultant contraction is larger and longer lasting. There is spasticity—an increased resistance to passive movement. In the bladder, this can be made apparent by filling the viscus so as to stretch the musculature, while the pressure is recorded. This spasticity is thought to be due to increased reflex activity, the result of heightened stretch reflexes. Cystometrography at this time shows a more active detrusor musculature; the tone is increased, the pressure curve rises very steeply compared with the normal, and there are sharp waves of increased pressure. When these sharp waves occur, the sphincter mechanism of the bladder and urethra relaxes. Periodic micturition now occurs; and the urine can be manually expressed with relative ease. Thus, retention of urine with decreased reflex activity changes to periodic automatic micturition. This periodic micturition can be so efficient that the bladder may expel all its contents. Eventually, posture, as designated by Sherrington above, becomes conspicuously absent; for much spontaneous change in pressure occurs with a constant volume of fluid. The pressure is constantly high with a small volume of fluid; for instance, 75 ml. of fluid may be held at a pressure of 100 cm. of water. The reaction of the bladder musculature is now greatly enhanced. Sudden contractions of the musculature often expel the catheter as well as the urine. Anything causing the slightest increase in tension on the bladder musculature, such as a rise in intra-abdominal pressure, or a slight movement, gives rise to the micturition reflex—contraction of the detrusor with opening of the sphincters and expulsion of urine; but this reflex is inadequately sustained, so that although small amounts of urine are spurted out, large amounts often remain in the bladder. When the pressure of the bladder is very high, these reflex expulsions of urine may lead to the wrong conclusion that urine is dribbling away

continuously, as with a patulous sphincter. Cystometrography at this time shows a steeply rising curve in nearly all cases; however, in a few cases the curve remains flat once a certain high level has been reached.

The normal coordination between the detrusor musculature and the sphincter musculature is severely disturbed. Denny-Brown and Robertson (1933) have suggested that this is partly due to the fact that intercurrent stimuli from the lower part of the body cause a sudden reflex shutting of the sphincter with consequent cessation of micturition before the bladder has been emptied.

The progress through these recognized three stages is gradual. Stage I is the stage of absence of detrusor contractions and of the micturition reflex; Stage II is the stage of spasticity with a steeply rising cystometrographic curve; and Stage III shows the features of Stage II in more pronounced form; there is intense spasticity, vigorous contractions of the detrusor being evoked by small quantities of urine and by intercurrent stimulation of the more caudal parts of the body. This manner of considering the progress of bladder functioning as passing through three stages will be followed here, as it allows our work to be compared with previous work, and as it permits more concise presentation of our results.

Effects on Bladder Functioning of Cutting Spinal Pathways Subserving Micturition

It was said above: " When all the tracts subserving micturition have been divided, the resulting disturbance of function resembles that which occurs when the spinal cord has been totally divided." The slight differences in bladder functioning when the cord has been divided and when the spinal tracts specifically subserving micturition have been divided will now be considered.

(a) Sensation.—Patients with division of the tract conveying impulses subserving the normal sensation of the desire to micturate have nevertheless various other ways of finding out when the bladder is full and when it is going to evacuate its contents automatically. This aspect of the subject has been investigated and discussed by Nathan and Smith (1951) and by Nathan (1956 *a* and *b*).

(b) Conscious Control.—The ability to control consciously the levatores ani, and in particular their anterior parts, the pubo-coccygeus muscles, and the external sphincter is lost. How far this loss interferes with the ability to start micturition is not really known. In normal micturition the neck of the bladder descends in the pelvis and the anterior parts of the levatores ani contract and the detrusor contracts at about the same time; Nesbit and Lapides (1948) have shown that bilateral pudendal nerve block does not interfere with the ability to start micturition. With regard to stopping micturition, the external sphincter is important, and they showed that bilateral pudendal nerve block does interfere with this mechanism. It seems that one may state that without control of the perineal musculature the patient cannot start or stop micturition in a normal manner. However, such a patient when micturition has reached Stages II and III, may be able to empty his bladder, at least partially, by inducing a reflex contraction of the detrusor. Various ways of doing this are found by patients; they may press on the abdomen, hold the breath and strain, or they may flex the thighs and trunk. Although such a patient cannot actively stop micturition, it can often happen that micturition continues only as long as straining is sustained, and in such a case the patient can stop micturition merely by ceasing to strain. The normal inhibition of the rising pressure exerted by the bladder musculature, which is a feature of bladder control, can in no way be substituted when the relevant tract is divided. It is important to realize that the paralysis of the muscles of the pelvic floor and of the perineum can occur without any concomitant paralysis of the lower limbs, and with some neurological lesions one can find severe paralysis of the lower limbs with minimal involvement of the movements of the musculature of the pelvis and perineum.

(c) Postural and Reflex Activities.—There is no difference in these activities in those cases in which the cord is totally divided and in those in which only the relevant tracts in the cord are divided.

Such are the features of the functioning of the bladder to be found when the tracts within the spinal cord subserving micturition are divided. They can be made manifest in an acute experiment—observing the posture or tone of the bladder during the operation of dividing the relevant pathways in the cord, and in a chronic experiment—day-to-day observations of the postural and reflex activities after these tracts have been divided. Observations will not be made here on the sensory aspect of the subject as it has been considered in previous papers.

Methods of Investigation

Both the clinical and the histological methods of investigation employed were described in our previous paper on the afferent pathway in the cord (Nathan and Smith, 1951).

Material

Out of a series of 60 cases of cordotomy performed for the relief of pain in which full histological examination of the spinal cord and brain has been

carried out, 21 cases of bilateral cordotomy and 15 cases of unilateral cordotomy were studied in detail with regard to the functioning of the bladder and micturition; one case of thrombosis of the posterior inferior cerebellar artery was also investigated, although no post-mortem examination was made, the patient still living. The evidence from the other cases of this series supports the conclusions drawn from this selected material; but as these patients were not investigated in such detail, no further mention of them will be made.

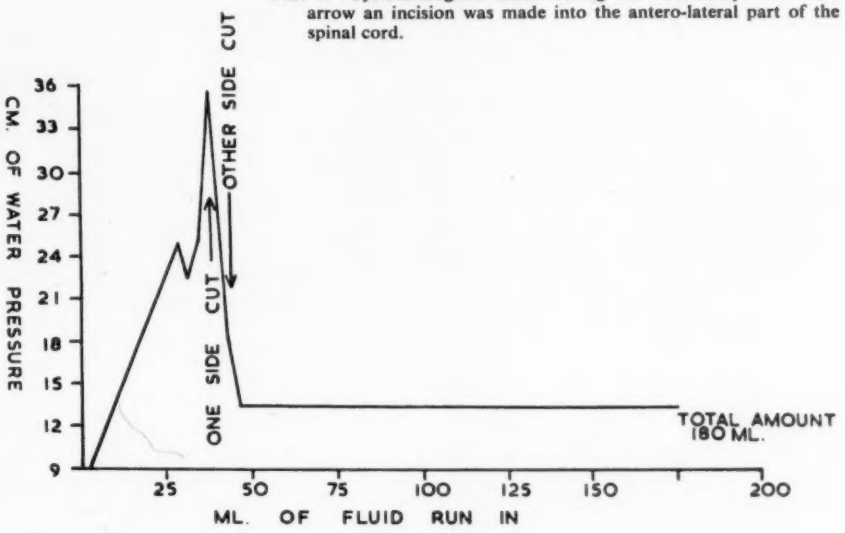


FIG. 1.—Cystometrogram made during the cordotomy. At each arrow an incision was made into the antero-lateral part of the spinal cord.

Although we now have a large number of cases, it is surprisingly difficult to collect a sufficient number of suitable cases for such a study as this. All the patients, except the one with a thrombosis of the posterior inferior cerebellar artery, had cancer. Patients in whom the cancer involved the central nervous system were excluded from the series; but those in whom only the peripheral nerves were involved had to be used. For in most patients needing cordotomy for the relief of pain the peripheral nerves are involved by the tumour. In some of these patients there was involvement of the sacral nerves on one side. It might be thought that as there was a lesion of the sacral nerves, the effects of dividing the pathway in the spinal cord could not be properly estimated; and it could further be objected that comparisons between cases cannot properly be made when some of the patients have the sacral nerves involved by growth and others have the peripheral nerve supply intact. And in addition to these objections, it might be considered that as the lesions made in the spinal cord vary considerably from case to case, the number of factors playing a role is so large that one case can hardly be compared with another. Nevertheless, it seems to us that the inclusion of patients with involvement of the sacral nerves on one side is justified. There is in this series a sufficient number of cases without any involvement of the sacral nerves, and so it is quite clear what the results of dividing the tracts in the cord are. A further reason is that each patient was investigated before and after the cordotomy; and so, whatever sort of bladder function was found before this operation, any sudden changes in it could be attributed to the effects of dividing the tracts in the spinal cord. And finally, the kind of bladder function that results from a lesion of the peripheral nerve supply is different from that kind which results from a lesion of the spinal tracts.

The Immediate Effects of Dividing the Tracts

An acute experiment demonstrating the loss of tone caused by sudden division of the lateral and antero-lateral parts of the cord is shown in Fig. 1 (Case 47). Cystometrography was performed during the course of the bilateral cordotomy; the anaesthesia was kept as light as possible to avoid any effects of the anaesthetic on the centres coordinating micturition. The pressure in the bladder was rising rather rapidly before the incision was made; this may have been due to the inevitable interference with the spinal cord. When one side of the cord was incised, the bladder pressure fell from 36 cm. to 18 cm. of water; when the second side of the cord

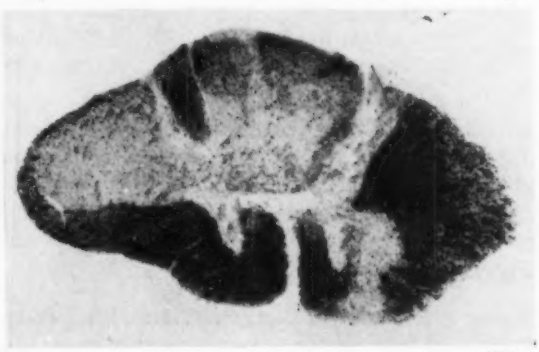


FIG. 2.—Case 47: Transverse section through lesion (Marchi preparation).

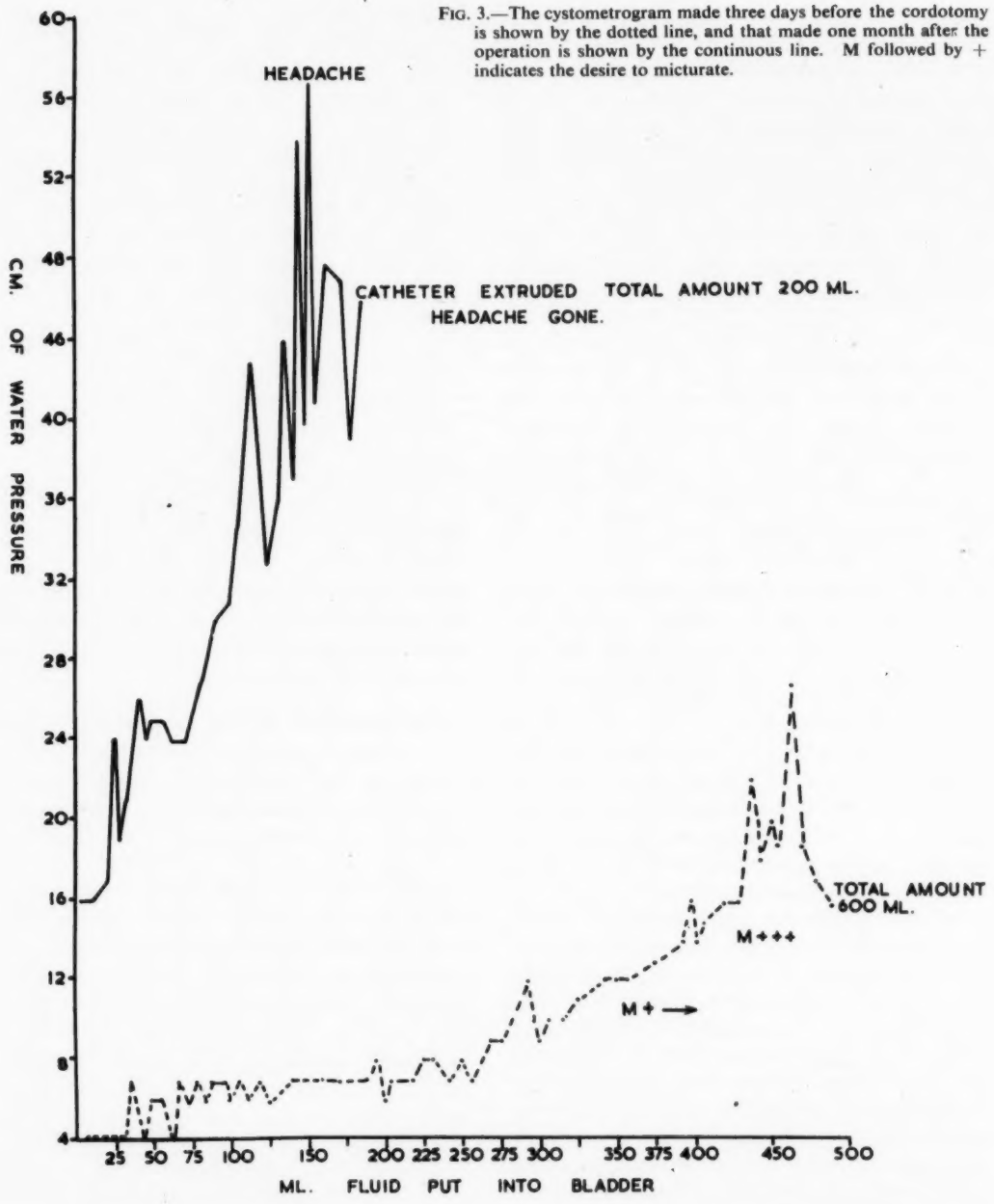


FIG. 3.—The cystometrogram made three days before the cordotomy is shown by the dotted line, and that made one month after the operation is shown by the continuous line. M followed by + indicates the desire to micturate.

was incised, the bladder pressure fell a further 5 cm., and it remained at this level for the rest of the time of the operation, in spite of filling of the viscus.

The extent and location of the lesions made in this spinal cord, in the thoracic segment, can be seen in Fig. 2.

Chronic Effects of Dividing the Tracts Bilaterally

Two cases will be described in which there was good evidence of bilateral division of all descending tracts.

Case 1.—Mrs. M. had a bilateral cordotomy for the pain due to carcinoma of the cervix uteri. Following the operation there was analgesia throughout the right side of the body below the sixth thoracic dermatome and throughout the left side of the body below the ninth thoracic dermatome. The function of the bladder was that of Stage I; and three weeks after the operation 0·25 mg. of carbaminoyl choline chloride had no effect on the bladder. One month after the operation Stage II was reached. Fig. 3 shows the cystometrogram performed before the cordotomy, and that performed after the cordotomy during Stage II. Comparing the two, the

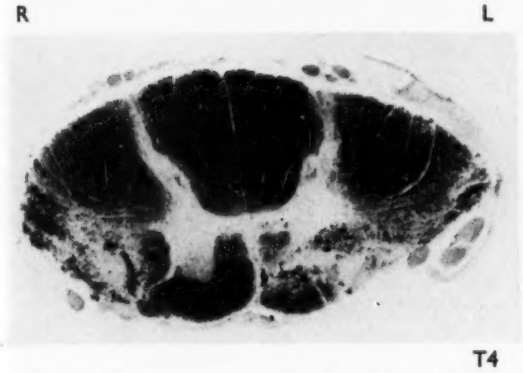


FIG. 4.—Case 1: Transverse section through lesion (Marchi preparation).

pressure on starting, when only enough fluid is in the system to take a reading, was 4 cm. before the operation, and 16 to 18 cm. after it. Before the cordotomy the pressure remained under 12 cm. as long as the contents were below 375 ml.; then, with the increasing desire to micturate, the pressure began to rise steeply. Strong detrusor contractions started when the bladder contained 500 ml. In Stage II, the curve showed no horizontal component; it rose steeply as the bladder was filled, and there were strong detrusor contractions throughout. Finally, when only 200 ml. was in the bladder, there was such a strong contraction that the catheter was extruded. Before the operation, as the bladder was filled the patient was making a conscious effort to hold urine; after the operation, she felt she could not influence the bladder in any way. At necropsy 68 days after the operation, the bladder was seen to be trabeculated.

The location and extent of the bilateral lesions in this case are shown in Fig. 4.

Case 7.—Mrs. Y had a bilateral cordotomy for the pain due to a colloid carcinoma of the cervix uteri. Following the operation there was analgesia throughout the right side of the body below the tenth thoracic dermatome and throughout the left below the eighth thoracic dermatome. The function of the bladder was that of Stage I; Stage II was reached 12 days after the operation.

The location and extent of the bilateral lesions in this case are shown in Fig. 5.

From these three cases—the two described immediately above and the one given to show the acute effects of dividing the tracts—deductions can be drawn on the location of the fibres used in the control and coordination of micturition. These cases were typical of the group; 16 of the 21 studied showed this complete syndrome. The smallest area of degenerating fibres common to the six sides of the three cords presented must contain the majority of the centrifugal fibres concerned in micturition. It can be seen from Figs. 2, 4, and 5 that this area lies on the equatorial plane of the cord. In all the cases in which there was the complete syndrome,

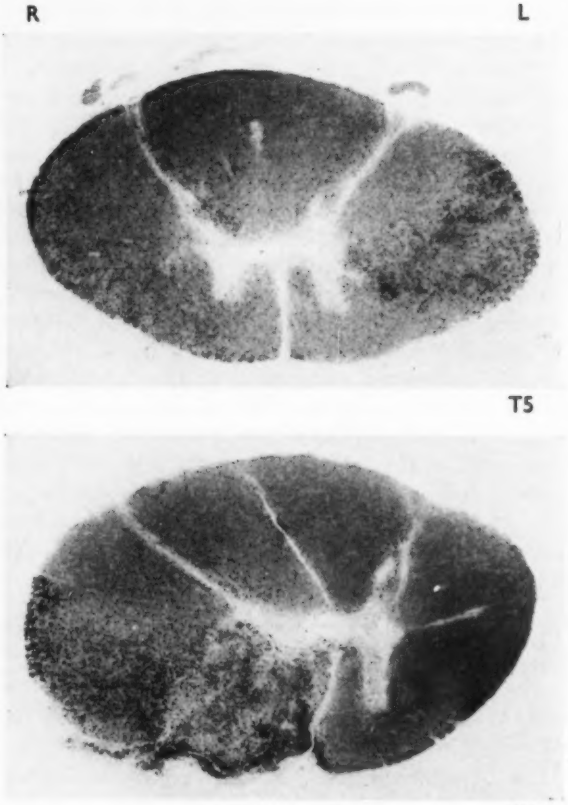


FIG. 5.—Case 7: Transverse section through lesion (Marchi preparation).

the lesions involved this region of the cord. In five other cases the typical syndrome was present for weeks, and then there was more recovery from this state than is usually found with complete lesions. It was interesting to note that in these cases the lesions made at operation did not involve this region as completely on both sides of the cord as it did in those cases with the complete clinical syndrome.

We thus conclude that the majority of the centri-

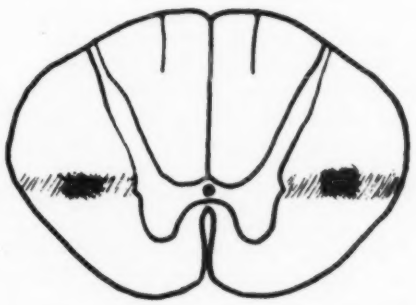


FIG. 6.—The region within the spinal cord of the centrifugal pathway for micturition. The majority of the fibres probably lie within the region indicated by cross-hatching.

fugal fibres descending from the brain must lie in this region of the lateral columns shown in Fig. 6.

In most of our cases, and in those presented so far, the lesions were made in the thoracic cord. In one case the incisions were made at the fifth and sixth cervical segments, and in two cases at the first and second lumbar segments. The location of the lesions in these three cases showed that the efferent pathway lies in the same region of the lateral columns in these parts of the cervical and lumbar cord as it does in the thoracic cord.

More evidence that the pathways lie in this part of the cord can be obtained from those patients who did not have the syndrome of complete division of the tracts but showed a part of the syndrome or more recovery from the stages of the syndrome than is possible with total division of the relevant tracts. Further evidence is also gathered from those patients who had the incisions made in the neighbourhood of these tracts, and yet had no disturbance of bladder function.

Chronic Effects of Partial Division of the Tracts Bilaterally

The following case shows that bilateral lesions anterior to the region shown in Fig. 6 do not cause the complete syndrome.

Case 21.—Mr. M. had a bilateral cordotomy for the pain due to a chondrosarcoma of the ilium. Although the operation was bilateral, the incision on the left side of the cord was made purposely superficial and somewhat anterior. Following operation there was complete analgesia throughout the left side of the body below the ninth thoracic dermatome, and hypoalgesia on the right side of the body below the ninth thoracic dermatome. For the first week after the cordotomy there was complete retention of urine. By the end of the first fortnight, however, except for some frequency of micturition, bladder functioning was normal. He could micturate without straining and he could stop micturating in the middle of the act; he could hold urine for half an hour or more after feeling some desire to micturate. This state continued for five months. After this time, it was seen through the cystoscope that the base of the bladder was involved in the spreading tumour; and so further conclusions on bladder functioning could not be attributed solely to the lesions in the spinal cord. The lesions in the cord of this case are shown in Fig. 7. It is probable that on the left side some of the relevant fibres have been cut and that on the right side they have not been involved.

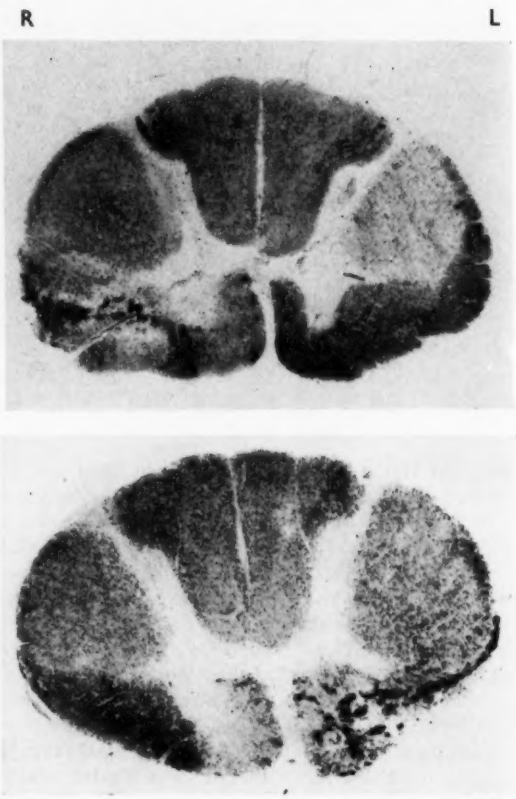


FIG. 7.—Case 21: Transverse section through lesion (Marchi preparation).

No Effects after Bilateral Lesions in Neighbourhood of the Tracts

The following case shows that bilateral lesions posterior to the region shown in Fig. 6 do not cause the syndrome.

Case 22.—Although the operation was bilateral, the incision on the left side of the cord did not involve any sensory fibres. Following operation, the only part of the body where pain sensibility was diminished was on the left in the first and second sacral dermatomes; it was slightly diminished in the third sacral dermatome. The

FIG. 8.—Case 22: Transverse section through lesion (Marchi preparation).

FIG. 9.—Case 11: Transverse section through lesion (Weigert Pal preparation).

patient developed no disturbance of micturition of any sort; he never had to be catheterized, he could start and stop micturition when he wanted, and he passed a normal amount of urine at normal intervals of time. The lesions in the cord are shown in Fig. 8. It will be seen that the equatorial plane is not involved, with the possible exception of a few fibres on the right side.

Thus Cases 21 and 22 serve to show the boundaries of this region where the centrifugal fibres are thought to run. In Case 21 the lesion on the right side is at the anterior limit of the region; and in Case 22 both lesions probably lie just posterior to it. Other cases with lesions not involving this region of the spinal cord showed no disturbance of micturition or its conscious control.

In a previous paper (Nathan and Smith, 1951) on the afferent pathway from the bladder, we showed that the afferent pathway lies in the same region as that which we are now proposing for the efferent pathway. In one patient, Case 11, there was clinical evidence of bilateral division of the afferent tract with only partial involvement of the efferent pathway. The lesions in the cord, shown in Fig. 9, involved the lateral part of the region shown in Fig. 6. Thus, this one case may be regarded as evidence suggesting that the centripetal pathway lies lateral to the centrifugal pathway.

We have now shown where the tracts lie in the cervical, thoracic, and lumbar regions of the cord. It remains to consider their position in the sacral region. Fig. 10 shows the distribution of the degenerating fibres in the lower lumbar and the sacral segments, following a unilateral cordotomy in the third cervical segment. Degenerating fibres are seen in the lateral column of the lumbar section and considerably fewer fibres are to be seen in the same region of the sacral segments. When a comparison is made between this case and other cases with lesions involving slightly different parts of the lateral columns, it is seen that the more anterior of the degenerating fibres shown in Fig. 10 are those concerned with the conscious control and coordination of bladder functioning.

Degeneration in fibres to the sacral micturition centre is accompanied by degeneration in descending fibres to the neurones for the lower limbs. But as the neurones for the limbs are situated mainly cranial to the third sacral segment, there are, among those degenerating fibres still present at, and caudal to this segment, the fibres concerned with micturition, defaecation, and the pelvic musculature. In our series of cases only a few fibres are to be seen at these levels; and even in the cases in which the cordotomies were performed in the lumbar region more fibres are not seen. This reduction in the

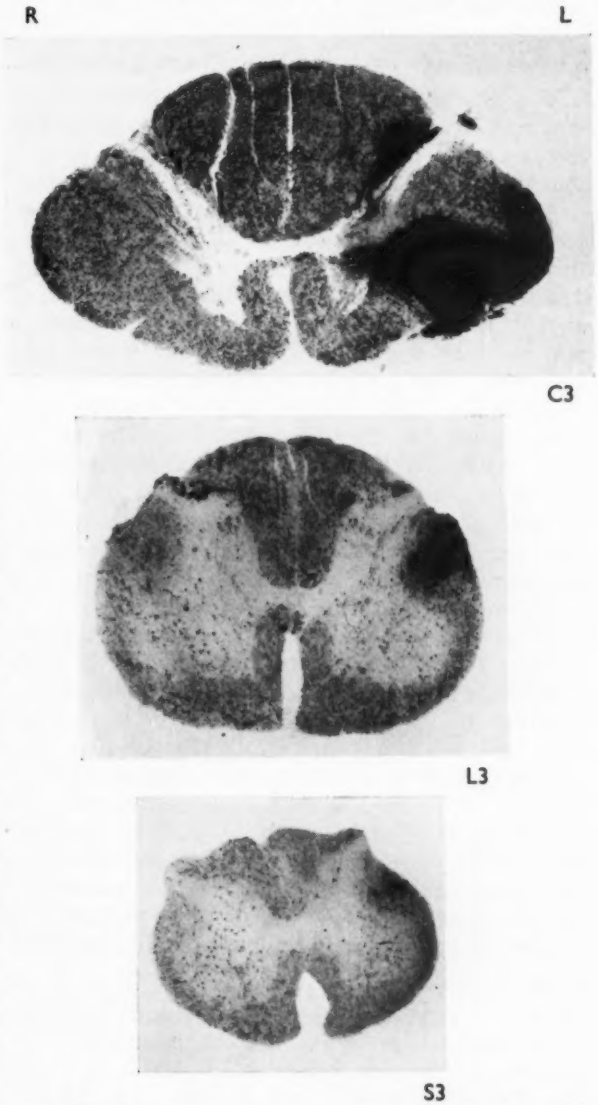


FIG. 10.—Case 37: Transverse section through lesion in cervical segment, and sections showing resultant degeneration in lumbar and sacral segments (Marchi preparation).

number of fibres between the lumbar and sacral regions may seem surprising. The reasons for the small number of degenerating fibres are probably the following. As is well known, the degeneration of the terminal parts of the axon is completed much sooner than that throughout the rest of the axon, and so the terminal parts cannot always be seen in those cases where degeneration can be traced throughout the rest of the tract. Also, it could be that a few of the centrifugal fibres relay in the grey matter of the cord between cervical or thoracic segments and the sacral segments; in this case, there would be no degeneration in the axons having their cells of origin caudal to the axons divided in the cordotomy lesion.

Chronic Effects of Division of Tracts Unilaterally

The clinical picture resulting from division of the tracts on one side of the cord can now be given; for in certain cases it can be shown histologically that the relevant tracts have certainly been divided.

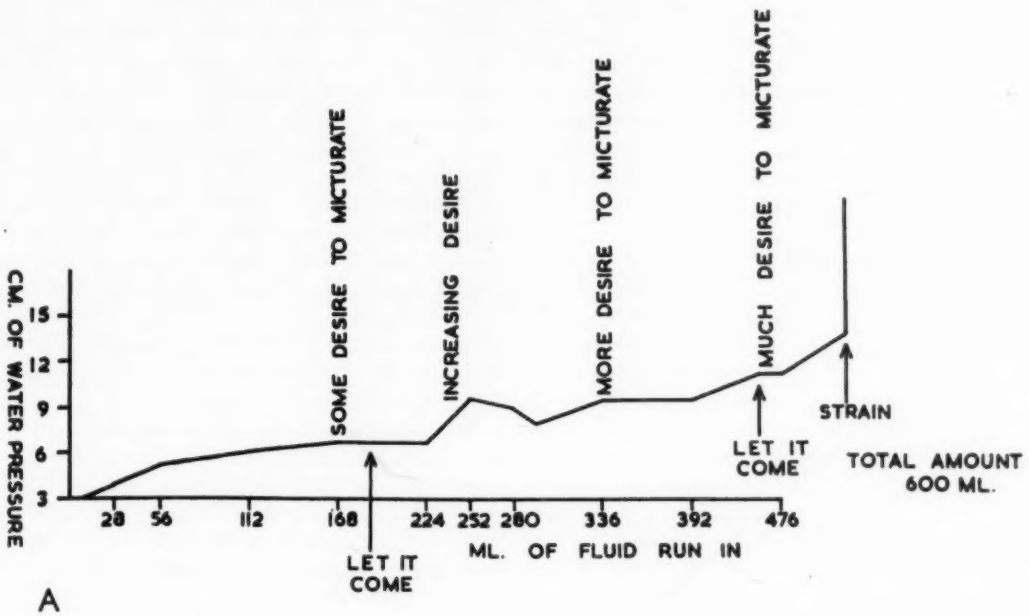
All patients who had the pathway subserving control of micturition divided unilaterally had no disturbance of voluntary control. Thus, one may conclude that a tract on one side of the cord is enough to ensure the normal function of starting and stopping micturition. (Needless to say, this statement is true only if the peripheral pathway and the structures, such as the bladder, urethra, and levatores ani, are themselves free from abnormalities.) Normal voluntary control is not necessarily present for the first four or five days after the cordotomy; for during this time (and immediately after any operation on the spinal cord) there may be retention of urine. But after a few days normal control is regained.

All patients who had the pathway subserving the postural and reflex activities of the bladder divided unilaterally showed an alteration in these functions. Although the patients were themselves unaware of any abnormal functioning of the bladder, an abnormality could be demonstrated by comparing the pre- and the post-operation cystometrograms: in all these patients the post-operation differed from the pre-operation one, even though the post-operation one came within normal limits. In all cases the difference consisted of a higher vesical pressure on starting filling and a high pressure throughout filling.

Case 37.—This will serve as an illustration of the clinical picture found with division of the tracts unilaterally. The cystometrograms made a week before and a fortnight after the operation are shown as Figs. 11A and B; and the extent of the lesion made at operation is shown as Fig. 10. The cystometrogram (Fig. 11A) made before the operation is essentially normal; and the patient had no history to suggest any sort of abnormality of bladder functioning. Immediately after the operation, he had almost complete retention of urine; after an injection of carbaminoyl choline, he passed 120 ml., but a further 800 ml. remained in the bladder and had to be removed by catheter. For five days he was treated by tidal drainage. On the sixth day, he had a definite normal desire to micturate, he strained, and urine was passed beside the catheter. Tidal drainage was discontinued. Micturition from this time was apparently normal. The patient had a normal desire to micturate, he could feel urine passing and could feel the muscles of his perineum acting. He could micturate without straining, could start when he wanted to, and could stop in the middle of the act. The cystometrogram (Fig. 11B) made a fortnight after the operation is, however, far from normal. This is the typical cystometrogram of Stage II. On every occasion that the pressure rose, the patient had the desire to micturate, but felt it unilaterally. (This feature was described in our previous paper, 1951.) That he could control micturition is reflected in the rise of pressure to 20 cm. when he was told to try and micturate. The comparison between the cystometrograms performed before and after the operation is striking. After the operation, the smooth slowly rising curve of the normal has gone, the base line, such as it is, is raised throughout, and spontaneous contraction occurs repeatedly, starting when there is less than 50 ml. of fluid in the bladder. When this cystometrogram was made, the patient was unaware of having any disorder of bladder functioning, for he could control micturition normally. But the division of the pathway unilaterally has disturbed normal bladder tone and has heightened the micturition reflex so that it is triggered off by inadequate stimulation.

Thus unilateral division of the centrifugal tract conveying impulses serving to inhibit bladder tone gives a change in vesical pressure—a change similar to but less than that which follows bilateral division of the tract. This might have been expected. For presumably less impulses arrive at the sacral centre from the centres in the brain, and so the total behaviour of the bladder resembles more nearly that of the bladder in cases of total cord division.

Cases of thrombosis of the posterior inferior cerebellar artery also show the syndrome of division of the tracts unilaterally. Although we have naturally not had the opportunity of performing cystometrograms before the thrombosis in such cases, cystometrograms performed after the thrombosis are similar to that given in Fig. 11B. The patient is usually unaware of any abnormality of bladder function, but the pressure is abnormally high, and the micturition reflex tends to occur frequently and with a relatively small amount of urine in the bladder. It is clear from such cases that in the medulla oblongata the fibres associated with the postural and reflex activities of the bladder must lie somewhere in the region between the inferior cerebellar peduncle and the olive, lateral



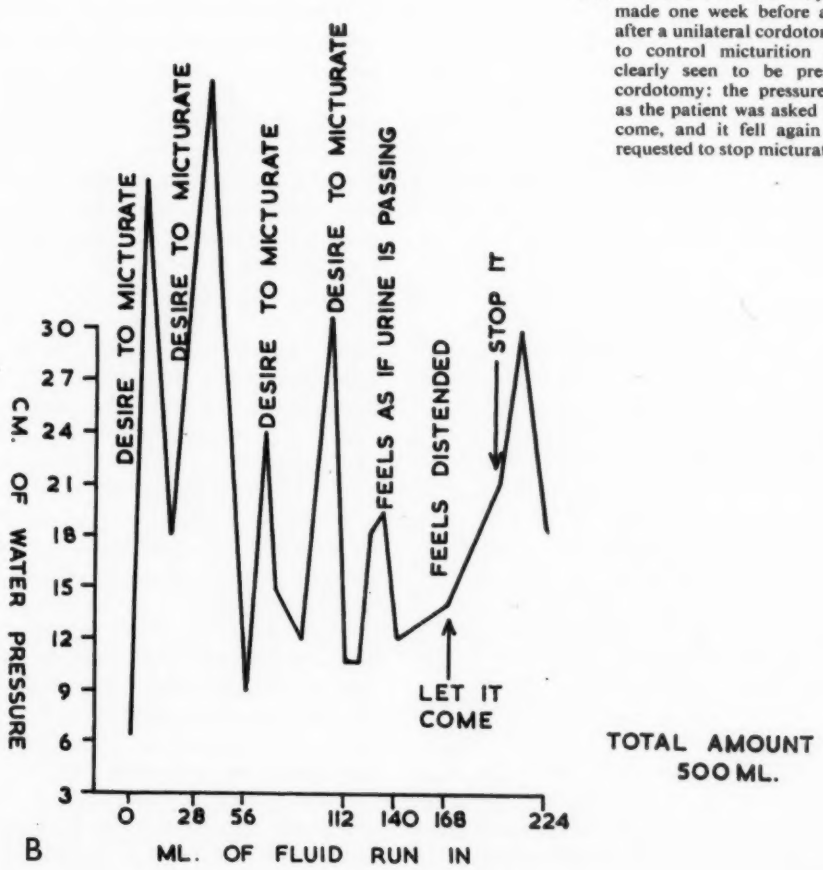


FIG. 11A and FIG. 11B.—Cystometrograms made one week before and two weeks after a unilateral cordotomy. The ability to control micturition on request is clearly seen to be present after the cordotomy: the pressure rose as soon as the patient was asked to let the urine come, and it fell again when he was requested to stop micturating.

to the twelfth nerve. This is a region known to contain many fibres arising in the reticular substance, including reticulo-spinal fibres. At this level the more exact location of the fibres concerned with micturition cannot be worked out from our material. It may be concluded, however, that the fibres concerned do not form a part of the cortico-spinal tract.

Conclusions

The following conclusions may be drawn from our evidence. In man, the majority of descending fibres concerned with micturition lie in the lateral column, on an equatorial plane passing through the central canal. This location remains the same in the cervical, thoracic, lumbar, and sacral segments. These are the fibres mediating conscious control of the perineal and pelvic musculature, the fibres necessary for the starting and stopping of micturition, those concerned in inhibiting micturition, and those that inhibit the independent activity of the sacral bladder centre. It may be concluded that these fibres do not run in the median longitudinal bundle, the tecto-spinal tract, nor the vestibulo-spinal tract, for these tracts do not lie in the equatorial plane.

The centrifugal fibres run in close association with the centripetal fibres from the bladder subserving the sensation underlying the desire to micturate, and with the fibres subserving defaecation. We have previously shown (Nathan and Smith, 1951, 1953) that the afferent fibres from the bladder and rectum lie in the lateral part of the lateral column, approximately on the plane of the central canal. The centrifugal fibres concerned with micturition are now shown to lie in the same plane, in a slightly more medial position; in the sacral segments, however, some of the efferent fibres lie on the periphery of the cord. We have been unable to separate the fibres concerned with conscious control from those concerned with the automatic, unconscious aspects of micturition. We have found some indication of a separation of the spinal fibres subserving defaecation from those subserving micturition. But the nature of our material—where the lesions made by the surgeon have to be large, and in which many of the patients have carcinoma in the pelvis—does not allow us to draw satisfactory conclusions about any differences in location of the fibres subserving these two functions.

Discussion

It has been shown that in man a bilateral operation on the spinal cord which divides the region on an equatorial plane passing through the central canal has an effect upon micturition similar to that produced by a complete transection. Using the same technique, Barrington (1933, 1948) found the tracts run in the same region in the cat. Czyhlarz and Marburg's (1900) suggestion that these descending fibres run in man in the neighbourhood of the cortico-spinal tract is supported by our evidence, but their belief that " in order to get permanent disorder of bladder function " both cortico-spinal tracts have to be damaged to a large extent was not justified by our experience. Langworthy and Lewis's (1935) conclusion from two cases of disseminated sclerosis without post-mortem evidence that these tracts probably run in the lateral columns of the spinal cord in the neighbourhood of the cortico-spinal tracts is shown to be correct.

We observed in some patients more evidence of recovery than occurs after total division of the cord. Foerster and Gagel (1932) and Foerster (1936) state that they found this also. They concluded that there must be other tracts in the cord subserving micturition which had not been divided by the bilateral cordotomy incisions, and they thought that such tracts must run elsewhere than in the anterior or the antero-lateral columns. The argument, it would seem, is not so simple. To show that other efferent fibres are functioning, it is necessary to show that in all cases micturition recovers more than it would after complete section of the cord. However, even with total cord transection, bladder functioning eventually appears to be fairly efficient. And furthermore, somewhat better functioning after division of only the lateral columns is to be expected than after total cord transection, for it is likely that other mechanisms are at the disposal of these patients, analogous to the trick movements used by patients with total divisions of peripheral nerves. For instance, they may have adequate information from the urethra to tell them that micturition is starting, progressing, and stopping, and they can take steps accordingly. In fact, experience has shown us that such patients sometimes have the impression that micturition is normal, when in fact all the spinal cord pathways are divided. They may notice only some degree of urgency. To the questions, Do you know when you need to pass urine, can you start micturition when you want to, can you stop passing urine in the middle of the act, the answer in each case can be, yes. And yet the patient may know when he needs to pass urine by paying attention to one of the substitute sensations, having lost the normal sensation underlying the desire to micturate; he may be able to start passing urine by means of increasing the intra-abdominal pressure or flexing forward while pressing his hands on his lower abdomen, having lost the normal mechanism; and he may be able to stop passing urine in the middle

of the act, as he may have that kind of micturition which needs straining to be kept up throughout the act; if he ceases to strain, he ceases to pass urine; but he has lost the normal active contraction of the perineal muscles and sphincters that is needed to interrupt micturition in the normal way. If in any patient there is definite evidence that the recovery of bladder function has gone beyond what is possible with total division of the pathways subserving micturition in addition to the aid provided by an otherwise intact nervous system, then one is justified in believing that some pathways are intact. It is more reasonable to suppose that the fibres which have not been divided lie immediately adjacent to the area of the lesion made at operation than to conclude that they do not lie in the anterior or the antero-lateral columns as Foerster did. The reason for saying this is that all the patients we have seen went through the typical stages of bladder function that occur following complete division; if some then recovered to a more normal condition, it would seem that originally all the fibres were affected, but that some on the periphery of the lesion were only temporarily put out of action.

It might be objected to our argument that as in almost all our cases the centripetal pathway in the cord was divided at the same time as the centrifugal pathways, it is wrong to attribute all the effects we have described to the division of the centrifugal pathways, for they might be due to an inadequacy of information on the state of the bladder being received at the centres cranial to the spinal cord. But this objection seems to us to be invalid for three reasons. The behaviour of the bladder following division of these tracts is identical with that of somatic musculature following division of the relevant descending tracts. Both show a period of spinal shock, followed by a period of reflex hyperactivity and spasticity, and both show paralysis or severe paresis of consciously controlled movements. It is known that these effects on the somatic musculature result from the removal of the influence of the descending tracts. Further, the fact that in those cases in which the relevant tracts were cut unilaterally there was an increase in the tone of the bladder musculature would tend to implicate the descending tracts as responsible for these changes rather than the centripetal tracts; for it seems very likely that one afferent pathway intact on one side of the cord would suffice to convey information from the bladder to cerebral centres adequate for the normal coordination and control of micturition. Finally, Case 11, of which the cord is shown in transverse section as Fig. 9, is important from this point of view; for this patient never regained the normal desire to micturate, the afferent pathways being divided, yet the tone and the reflex activities of the bladder returned to normal; and so here we had a case showing division of the spinal afferent pathways with normal bladder posture and coordination.

Summary

The location within the human spinal cord of the tracts subserving conscious control of micturition and the tracts subserving coordination of bladder functioning is determined.

These tracts are within the lateral column throughout the length of the spinal cord. Their approximate location is on an equatorial plane reaching from one periphery of the cord to the other, and passing through the central canal.

We wish especially to thank Mr. Wylie McKissock for his wholehearted cooperation. We are also grateful to the other neurosurgeons who have helped us and particularly to Mr. J. O'Connell. We would also like to thank Dr. E. A. Carmichael who gave us encouragement in this work and provided the facilities for it. To our technical assistants, Miss Anne Ebborn and Mr. K. L. Frampton, we would like to express our gratitude for their careful and painstaking work.

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LANGUAGE DISORDER IN A CASE OF KORSAKOFF'S SYNDROME

BY

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In 1935, Curran and Schilder drew attention to the incidence of a peculiar language disorder in cases with acute cerebral disturbances of traumatic or toxic origin. This disorder comprised misnaming, paraphasia, discursive and incoherent speech, and in some cases bizarre forms of verbal expression reminiscent of schizophrenia. Although the phenomena were ascribed in part to focal dysphasia, the authors commented on their similarity to certain types of language derangement occurring in the primary psychoses. Following Kleist (1914, 1934), they were led to place emphasis on the probable role of cerebral dysfunction in the genesis of language disorders in general.

In studies of post-traumatic confusional states undertaken during the war, Paterson (1942, 1944) was likewise impressed by the frequency of paraphasic speech disorders. He pointed out that although not all confused patients present a disturbance of speech, in those who do the picture differs in no essential way from that shown in cases of focal lesion without confusion, *e.g.*, in jargon aphasia. Indeed in several of his cases clear-cut dysphasic residua long outlasted the acute confusional state. At the same time, it was suggested by Zangwill (1945) that the speech disorder in certain of Paterson's cases appeared to transcend an ordinary dysphasia and to involve an underlying derangement of the thought processes.

More recently, Weinstein and Kahn (1952) have devoted a paper to paraphasia in organic brain disease. Their observations are based on a series of 30 cases in which misnaming and other peculiarities of language were prominent. These disturbances, they point out, never occurred in isolation and were always associated with disorientation, denial of illness, and related symptoms of general organic type. The intracranial lesions consisted mainly of deeply situated or bilateral tumours, and aneurysms with subarachnoid haemorrhage; in nearly all cases the E.E.G. showed bilateral diffuse delta wave activity. The authors argue that the language disorders observed in their patients differ in important respects from those ordinarily met with in aphasia. For instance, words are not garbled and the rhythm of speech is normal. Further, misnaming was commonly referable to concomitant disorders of perception and orientation, and did not necessarily presuppose derangement within the sphere of language itself. Emphasis is also placed on the role of motivational factors, more especially those presumed to govern denial of illness. In conclusion, the authors argue that paraphasia in cases of organic brain disease should not be classed as an aphasic disorder referable to a focal lesion of the dominant hemisphere. It is to be regarded as the manifestation of a more general change in behaviour, in which altered patterns of perception and motivation play an important part.

In the analysis of confusional states it is obviously important to ascertain whether, and if so to what extent, focal signs and symptoms contribute to the overall picture. Although the attempt made by Paterson (1944) to explain confusion as a mere aggregate of focal signs may well appear too atomistic, the conception of a global organic reaction-type advanced by Weinstein and Kahn (1952) undoubtedly goes too far in the opposite direction. As Paterson has pointed out, the confusional state is always an individual affair and shows very considerable variation from case to case. In particular, by no means all confused patients exhibit paraphasic speech and the latter does not appear obviously related to the depth or severity of confusion. Further, defects of orientation (Paterson, 1944) and denial of disability (Critchley, 1953; Brock and Merwarth, 1957) are often particularly prominent in cases in which the lesion principally involves the parietal lobes. It might therefore seem probable that both general and local changes in cerebral function contribute to the confusional state and that these, in combination, determine the incidence of paraphasia. At all events, one may suggest that fuller analysis of language and its disorders may throw light on the psychology of confusional states.

We propose in the present paper to attempt a preliminary analysis of the disorders of thought and

language encountered in a case of Korsakoff's syndrome. It is hoped first, to determine whether the disorders in question are or are not referable to focal dysphasia; and secondly, to ascertain their relationship to concomitant changes in other spheres of psychological function.

Case Report

N. H. (Case No. 66352), a British Railways clerk, aged 62, and right-handed, was admitted under the care of Dr. Purdon Martin with complaints of episodic double vision, weakness in the legs, and numbness and coldness in the fingers of both hands of six months' duration.

One week previously, he had begun to "wander" in his mind, talking of the past and claiming to have recently seen his parents and other relatives long dead. He had become sleepy and difficult to rouse. There was also a history of recent loss of appetite, and of long-standing alcoholism.

On examination, the patient was facile, euphoric, and much given to confabulation. His speech was remarked to be nonsensical on occasion. He was disorientated in all spheres, believing himself to be in a flat in the vicinity of a hospital and the other patients to be railway workers. He gave the day (Monday) as Friday and the month (June) as May. His general knowledge and recent memory were very poor and insight was completely lacking.

On neurological examination, the main findings were unequal pupils, the right being slightly larger than the left, and some nystagmus, with impaired conjugate deviation in all directions. Convergence, on the other hand, was relatively well preserved. There was some loss of muscle power in the distal parts of the limbs but the most striking finding elsewhere was extreme tenderness of the muscles, with peripheral impairment of all forms of sensation. The tendon reflexes were uniformly diminished.

A diagnosis of alcoholic peripheral neuropathy with Wernicke's encephalopathy was made and some of the symptoms gradually settled down with large doses of B group vitamins. The eye signs were the first to clear; several weeks later the patient was again ambulatory and made few complaints of paraesthesiae. The results of liver function tests were relatively normal, but a histamine test meal revealed the absence of free acid in the stomach.

The patient was first seen in the Psychological Department two weeks after admission and thereafter re-examined at regular intervals until discharge.

He was at first completely disorientated for place and person, commonly believing himself to be in his usual place of work or at a clinic near his home. On one occasion, however, he thought he was on a Channel steamer bound for France. Persons were consistently misidentified in the light of his prevailing disorientation. Memory for recent events was virtually nonexistent and the patient confabulated freely. He showed also a patchy retrograde amnesia extending over some 10 years before the onset of the illness, though without clear-cut boundaries. His mood was in general euphoric, though this became less marked during the last few weeks in hospital, when the patient also regained some measure of orientation. He was facile and totally without insight, denying that he was ill or that his memory was in any way affected. In all these respects his mental state approximated to that of the classical Korsakoff psychosis.

Although the patient's speech appeared essentially normal in ordinary conversation, a curious paraphasic disorder was in evidence during the earlier stages of the illness. This was brought out most strikingly when the patient was asked to name objects, define words, explain proverbs or to undertake kindred tasks implying some measure of directed thinking (see below). There were also signs of a minimal defect in comprehension of speech at this time. Although the patient's hearing was in no way defective, he commonly asked for questions to be repeated and it was sometimes apparent that he had not fully grasped their import. Occasionally, he appeared completely at a loss for the meaning of a common word. He was, however, able to write with reasonable adequacy and showed no obvious defect of letter formation or spelling. Apart from want of sustained attention, reading did not appear to be affected.

These language disabilities receded very considerably during the last weeks of the patient's stay in hospital.

Formal psychometric testing gave an uneven picture. The vocabulary score was just below the mean, but this may have been in part due to the language disability. Performance on other Wechsler-Bellevue subtests suggested an I.Q. in the region of 110. Despite his amnesia, the patient could repeat seven digits forwards and five backwards. He was unable to solve Weigl's test, sorting being inept and concrete. Performance on a Rorschach test was grossly perseverative and typical of an organic confusional state (Zangwill, 1945).

Air encephalography indicated a marked degree of cerebral atrophy: good filling of the ventricular system was obtained and the system was observed to be central. The lateral ventricles showed a marked degree of generalized symmetrical enlargement. There was a considerable increase in the size of the cortical subarachnoid channels and the basal cisterns were a little enlarged.

The patient was discharged to another institution four months after admission. Although the brain-stem disturbances and peripheral neuritis had improved appreciably, the underlying Korsakoff state remained unaltered.

Follow-up Studies.—The subsequent history of the patient is briefly as follows. He remained for four and a half months in hospital, during which time he made some progress, becoming gradually more lucid and less given to confabulation. He then discharged himself against the advice of his physicians. He had since remained at home and had not attempted to return to work.

The patient attended for a follow-up psychological examination 16 months after his discharge from the National Hospital. He was found to be lucid and approximately orientated in all spheres. He did not now misidentify persons. Although his memory for recent events was still grossly impaired, he no longer con-

fabulated. There was, however, marked amnesia for events which had preceded the onset of the illness by some five to 10 years. The patient still lacked insight and denied his defect of memory. At the same time, he was considerably less euphoric than at the time of his discharge.

The patient's wife reported that he was strikingly unconcerned about his general situation but had otherwise shown no gross personality change.

In conversation, speech was fluent. Syntax and grammar were correct and choice of words appropriate. The patient could read aloud without hesitation or error. Nonetheless, he still appeared a little slow in grasping information and might still ask for questions to be repeated. He named objects correctly—with the exception of a drawing-pin which was miscalled a safety-pin. There was no apraxia.

On mental tests, it was found that the patient was unable to learn the Babcock sentence with 10 trials or to reproduce the gist of the cowboy story after two repetitions. On the other hand, pictures were described and interpreted in normal fashion and simpler block design tests adequately executed. Slight conceptual weakness was in evidence in Weigl's sorting test. Explanation of idioms and proverbs was now more satisfactory, although paraphasic and otherwise inappropriate responses might still be given. These contrasted strikingly with the patient's ability to describe pictures or to conduct an ordinary conversation.

Apart from the persistent minimal language derangement, the patient's state at this time appeared typical of a residual alcoholic Korsakoff psychosis.

Analysis of Language Disorder.—A number of interviews with the patient were recorded verbatim and analysed in some detail. A tape-recording of his conversation during the period of gross confusion was also made. The principal findings are as follows:

Misnaming.—In ordinary speech, names were used for the most part appropriately. On object-naming tests, on the other hand, the patient's responses were often grossly abnormal. The following examples may be given:

(19.7.56) *Watch*—Wrist-watch. *Cigarette lighter*—top hat lighter; asphalts and all that—tobacco accessory. *Penknife*—knife . . . jerry-knife, horse-knife as well. *Corkscrew*—an automatic accessory for bunging beers out of bottles. *Pipe*—pipe. You smoke it.

(31.7.56) *Penknife*—smoke affair. *What is that* ? smoke button. *Spanner*—poetic collector. *What is it used for* ? Sharpening a knife. In and out, round the corner.

(9.8.56) *Biro*—a fountain pen but what we now call a box fountain pen. *Box of matches*—relief pens; matches of course. *Bunch of keys*—major keys, for use with any major fountain pen issued. I hope without keys. We call them vellum. I think that's what the name was when they were first put out.

Paraphasia and Neologisms.—A striking feature of the patient's speech was his tendency to use long and unusual words in quite inappropriate ways. Thus he referred to an interview as a " psychoanalogical categoreal examination " and gave as his reason for being in hospital that he was " suffering from expectorations of cholera attacks ". In explaining a proverb, he referred quite irrelevantly to " an antagonistic outlook they've got on the affiliated amount of medical experience they possess ". Occasionally, frank neologisms appeared in his speech, *e.g.* he used the word " cosmey " to denote a variety of wood and " stanch " to denote a meal.

These neologisms were fleeting and seldom, if ever, repeated.

Paraphasia was always much less apparent in ordinary conversation than under circumstances in which the patient was asked to define words, repeat phrases or explain proverbs, *i.e.* under conditions in which verbal reaction was relatively constrained. The patient appeared quite unaware of his paraphasias and made no attempt to correct them.

Perseveration and Discursiveness.—Perseveration both of words and ideas was frequent on verbal tests. More striking, however, was the patient's lack of thought control, expressing itself in flightiness, discursiveness, and a certain queer circumstantiality. Although his replies to direct questions were often brief and to the point, any task involving directed thinking provoked a long, discursive, and often totally incoherent flood of speech. This combination of paraphasia, discursiveness, and perseveration is well shown in the following examples drawn from his attempts to explain idioms and proverbs:

Safety First (9.8.56).—" I suppose it should mean to the ordinary person going up in education that it will mark your pen without any burn or flame or ink (perseveration from object-naming tests). You write on the paper but with safety without any accident that might occur afterwards."

(16.8.56) " It's an idea to make sure during any accident that is taking place. Light for the patient. First claim is made as the duty of the instruments used to make sure that the method is going to give you the results—perfect patient."

A bird in the hand is worth two in the bush (9.8.56).—" Well, a bird in the hand's a safety first giver (perseveration). It's a winner isn't it ? . . . . It's not birds it's something you wanted and effect desired and instruction given."

(16.8.56) " It means in the entirety of it, if you've got one in your hand you've got one. Two in the bush have their own leisure, freedom, patience—no contact with them. You could have one in each hand—would give you double the one."

Too many cooks spoil the broth (16.8.56).—" Too many quits ? Quits make an equal." (*Proverb repeated*): " Oh ! Too many cooks spoil the broth. I'm good enough to do the cooking without your assistance. Just a plain statement that goes out from the ordinary cook. An antagonistic outlook they've got on the affiliated amount of medical experience they possess."

Pedantry and Witzelsucht.—There was at times a curious pedantry in speech. On one occasion, for

instance, the patient named a rubber as " an india rubber or as you say in more obvious language an india rubber eraser ". Equally, the combination of euphoria with lack of thought control gave rise on occasion to a definite *Witzelsucht*. Thus a corkscrew was called " an automatic accessory for bunging beers out of bottles ". He referred to the examiner on one occasion as " Dr. Caversham Caversham " (he had attended at a clinic known as the Caversham Centre) and remarked, à propos of being in hospital, that " The doctor said ' The Guillotine Department for you ' ! "

The overall impression given by this patient's speech is difficult to convey. The flow of speech is exuberant, poorly controlled, discursive, paraphasic, and at times totally incoherent. Yet grammar and syntax are formally correct and there is no real nominal aphasia. The patient is much given to long and abstract words—the proper meanings of which were almost certainly unknown to him—and at times to a curious circumstantiality.

Bizarre trends are expressed from time to time and there is occasional *Witzelsucht*. The total picture is perhaps best described as a kind of confabulation within the sphere of language.

The language disorders which have been described could still be elicited when the patient was re-examined over a year later. At this time (February 27, 1958), the patient's speech was superficially normal, and in spite of amnesia and lack of insight he could scarcely have been called confused.

Safety First—" It's rather a lateral term which means it could apply to a host of things. A road for one thing."

Its meaning ?—" To my mind it means the primary thing in life is safety in any direction or walk of life, with traffic and so on."

Too many cooks spoil the broth—" That's rather an old saying. It could apply to quite a lot of things. Too many people poking their noses into other people's business. Actually it's got nothing to do with cooking or broth."

A bird in the hand is worth two in the bush—" Well, I should imagine it emanates from a safety point of view really. I imagine it could emanate from a safety point or traffic. . . ." (*Proverb repeated*): " It really emanates from a safety turn . . . everything in hand, from a safety point of view. Your position wherever you are going—walking, travelling, cycling, motoring—is fairly well preserved."

A rolling stone gathers no moss—" I'm afraid I'm like one myself now. . . I'm just rolling about now. I'm used to an active life . . .non compos mentis."

Although at least one of these proverbs is adequately explained, evidence of paraphasia, perseveration, and flightiness is still present.

Discussion

The language disorder in this case is closely parallel to that described by Curran and Schilder (1935) in their cases of toxic and traumatic confusional states. Its most noteworthy features are misnaming, paraphasia, discursiveness, perseveration, pedantry, and *Witzelsucht*. There was also an increased " speech drive " (logorrhoea) of the kind often reported to accompany sensory aphasia. The patient had no insight into the speech disorder and made no attempt to modify or correct his paraphasic errors. The language disorder receded very considerably in the later stages of the illness, despite the fact that the amnesic-confabulatory state improved much more gradually.

It is pertinent to inquire whether, and if so to what extent, this curious language disorder may be attributed to focal dysphasia. It is hardly necessary to point out that many features of this patient's speech are strongly suggestive of a jargon aphasia. Indeed we have records of cases of left temporal lobe lesion, without obvious defect of consciousness or memory, yet presenting almost exactly the same combination of logorrhoea, paraphasia, and perseveration. Further, the patient gave definite evidence of a mild comprehension defect, which in itself suggests low-grade central " word deafness ". Although specific involvement of the left temporal lobe has certainly not been established, there is at any rate *prima facie* evidence of a dysphasic element in the syndrome.

Nonetheless, the disorganization of language in this case presents features which would appear to go beyond a disorder of speech as ordinarily conceived.

There would seem to be a basic loss of orderly and coherent thought and an irresponsible use of language akin to confabulation. Indeed the picture might suggest in exaggerated form that " approximate " use of language to which attention has been drawn in some patients after standard prefrontal leucotomy (Petrie, 1952; Tow, 1955). In these cases there is not uncommonly repetitiveness, alliteration, bizarre and inadequate formulation, and occasionally frank paraphasia (Tow, 1955). More striking, perhaps, is the parallel between the speech disorders we have described and those reported by Kleist (1934) in certain cases of occipito-temporal brain injury. Kleist believed the disorder in such cases to originate at a level antecedent to that of formulation and choice of words, *i.e.* at the pre-verbal level of thought. He therefore regarded it as a disorder of thought (" paralogia ") rather than as a disturbance of speech (" paraphasia "). Although the relations between thought and speech are obscure, it would appear plausible to regard a derangement such as we have described as involving far-reaching disorganization of the thought processes.

The relation of the language disorder to concomitant defects in other spheres of psychological

function deserves brief mention. As we have seen, Weinstein and Kahn (1952) place great emphasis on the part played by perceptual and motivational changes in the genesis of confusional paraphasia. As regards perception, there are undoubtedly a few cases in which it would appear plausible to refer misnaming to faulty visual perception. For the most part, however, objects are misnamed despite a correct grasp of their nature and use. It is also of course true that persons and situations are constantly misnamed in accordance with the prevailing disorientation, as in the cases described by Weinstein and Kahn (1952).

Yet it would seem improper to classify these responses as " paraphasic " in the ordinary sense of the term. Given the patient's limited and erroneous grasp of his environment, misnaming of persons and places is a psychologically consistent response. Unlike the language disorder which we have described, it is a constant feature of the Korsakoff psychosis.

We were unable to find much evidence of motivational changes governing speech errors in the present case. True, the patient made considerable reference in his talk to medical topics, even while denying that he was in hospital or in any way ill. This might suggest an underlying concern with issues relevant to the illness despite ostensible denial. The influence of previous personality make-up may also perhaps be traced in the patient's strong tendency to confabulation, *Witzelsucht*, and irresponsible speech. Further, it is plausible to suppose that motivational trends may find disguised and bizarre expression in confusional states, as in dreams and psychosis (Paterson and Zangwill, 1944). Fuller analysis of " paralogia " in confusional states is obviously necessary before final conclusions can be drawn.

Summary

The occurrence of paraphasic speech disorders in organic confusional states is reviewed.

A case of Korsakoff's syndrome presenting a marked disturbance of language and thought is reported. This disorder is best described as a kind of confabulation within the sphere of language (" paralogia ").

The relation of the language disorder to focal dysphasia and to concomitant defects in other spheres of psychological function is considered.

We wish to express our sincere gratitude to Dr. J. Purdon Martin for his kind permission to study and record this case and for his advice in the preparation of this paper. We also wish to thank Dr. Isaac Sutton, Physician Superintendent, Friern Hospital, for his kindness in providing us with the follow-up information.

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THE SURGICAL SEPARATION OF SIAMESE TWINS CONJOINED BY THE HEADS (CEPHALOPAGUS FRONTALIS) FOLLOWED BY NORMAL DEVELOPMENT

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Human conjoined twins are rare. Various authors (Mortimer and Kirshbaum, 1942; Potter, 1952) give figures ranging from one in 60,000 to one in 85,000 births for various types of Siamese twins either alive or stillborn. In 117 conjoined twins, a series of which was compiled by Robertson (1953) from Taruffi's eight-volume study on heratology (*Storia della Teratologia*, Bologna, Regia Tipografia, 1881-94), thoracopagus was present in 86, pygopagus in 22, ischiopagus in seven, and cephalopagus in two only. From the analysis of these data it appears that the incidence of cephalopagus would be in the range of one in every two to four million births.

The only satisfactory treatment of cephalopagous twins is surgical separation. This, however, presents enormous technical difficulties and the number of surviving infants after such procedures are few. In the present communication we are therefore reporting an instance of Siamese twins who were conjoined by the frontal regions of the heads and who continue to develop normally after separation.

Case Report

Virginia and Tresea, 2-month-old female twins conjoined by the heads, were admitted to the National Institute of Neurological Diseases and Blindness for study and possible treatment in October, 1956. The mother was 21 years of age at the time of delivery. She has always been healthy. There were no multiple births in her family nor any evidence of neurological or developmental abnormalities. Her menstruation has always been regular. She has had three pregnancies, all resulting in live births. The first child, a girl 4 years of age, and the second child, a boy, 28 months of age, are normal in all respects.

The father died of rheumatic heart disease at the age of 39 years three months before the twins were born. There were no known instances of congenital malformation or any neurological condition in his family. One of the paternal uncles has dissimilar twins.

Present Pregnancy.—The mother received regular prenatal care from the second month of gestation. During the first two trimesters she was subject to nausea and minor headaches but no vomiting. About three weeks before the delivery the membranes ruptured spontaneously and approximately a quart of fluid escaped. She was admitted to hospital for a few days and then remained in bed at home having periodic minor uterine contractions. She was re-admitted to the hospital in Elizabethton, Tennessee, on August 9, 1956, and three hours later female Siamese twins were delivered. The total birth weight of the conjoined twins was 3·5 kg. The mother had general anaesthesia and does not know the details of the delivery nor the immediate state of the infants. She was told by the doctor that the second twin, who was slightly smaller (subsequently named Tresea), had to be resuscitated.

According to the physician attending the delivery there were two umbilical cords, one placenta, one chorion, and two amnions.

After two weeks in the hospital the twins were discharged home and for the next two weeks the mother fed them using a dropper. From the age of 1 month they were put on a bottle. In spite of great difficulty with feeding and general care, the mother had them at home until they were 2 months old.

Examination of the Twins at 2 Months of Age.—The infants were joined by the frontal and vertical regions in such a fashion that the predominantly right side of the head of one twin was in union with the predominantly right side of the other twin. In this way they appeared in mirror position to each other although slightly to the left (3 cm.) from the mid-sagittal planes (Figs. 1 and 2). The anterior fontanelles were partly open and partly involved in the bony union. The right orbital region and right eye were in close apposition, and when the infants were put in a parallel position the eyes were slightly compressed. The joined areas were in firm bony union. Tresea's joining part of the head appeared to telescope into Virginia's head forming a sort of coning (Figs. 3 and 4). The circumference of the conjoined area was 24 cm. The total weight of both twins was 4 kg. The state of nourishment and general physical conditions were good. They both took their feeds well. There was no evidence of other congenital abnormalities and their internal organs were normal. It was obvious that most

FIG. 1.—Siamese twins joined by the frontal region of their heads. The infant on the right is Virginia; the one on the left is Tresea.

FIG. 2.—The fusion of heads extends almost throughout the transverse diameter. Slight lateral shift of the otherwise mirror position of heads can be noted.

of the physiological functions of the infants were dissociated. One could be asleep while the other was awake and even crying. The rectal temperatures showed minor differences and also their pulse rates and respiration rhythms differed.

Virginia.—Virginia was the slightly bigger twin. Her head circumference, from the occiput to the top of the union at the vertex, was 34·5 cm. The bitemporal diameter was 8·5 cm., the antero-posterior 11·6 cm., and the vertical 7·2 cm. The chest circumference was 32·0 cm. She responded in the normal way to a flashing light in her eyes by tightening her eyelids and by following the lesser intensity of light to the left side and up. The fundoscopic examination showed normal discs and retinae. The pupils were equal and reacted to light. Both eyeballs showed a moderate degree of internal squinting and the right palpebral fissure appeared narrowed and compressed as a result of close approximation by the corresponding regions of their foreheads. There was no nystagmus. She responded to gentle ringing of a bell by a decrease in activity. The rest of the cranial nerves were normal. She showed vigorous spontaneous movements of all four extremities in all joints. She responded normally to painful stimuli. There was no evidence of tremors or abnormal involuntary movements. The tendon reflexes were all present and equal. The Moro reflex was fully developed and symmetrical. Tonic neck reflexes could not be tested. Hand and toe grasp reactions were well developed on both sides. She was able to retain briefly a toy inserted in either hand and her hands were predominantly open.

Laboratory Tests.—The blood group was 0, Rh positive. Haemoglobin was 11·9 g. The urine was normal (CO_2 content 28 mEq./l. serum chlorides 105 mEq./l., calcium 9·4 mEq./l., potassium 4·8 mEq./l., sodium 140 mEq./l.). A radiological examination showed a normal chest and normal size of abdominal organs. There were no congenital malformations or other abnormalities in the skeletal structure. A radiograph of the skull showed that the frontal region, predominantly on the right side, was in junction with the corresponding bony parts of the co-twin (Figs. 3 and 4). Even with the help of laminograms it was not possible to estimate the precise size of the bony defect between the adjacent two brains. An approximate estimation showed it to be about 5 cm. in diameter.

Tresea.—Tresea was the slightly smaller twin. Her head circumference from the occiput to the top of the union at the vertex was 33·5 cm. The bitemporal diameter was 8·4 cm., the antero-posterior 11·4 cm., and the vertical 7·8 cm. Her chest circumference was 29·5 cm. She followed light to the left and up and tightened her eyelids to a strong flashing light. Fundoscopic examination showed normal discs and retinae. The pupils were equal and reacted to light. There was a bilateral internal squint, more pronounced on the left. The palpebral fissure on the right was narrowed as a result of pressure by the excess of skin below the line of bony junction. There was no nystagmus. She responded to auditory stimuli by decreasing her activity. The facial sensation to pain and corneal reflexes was normal.

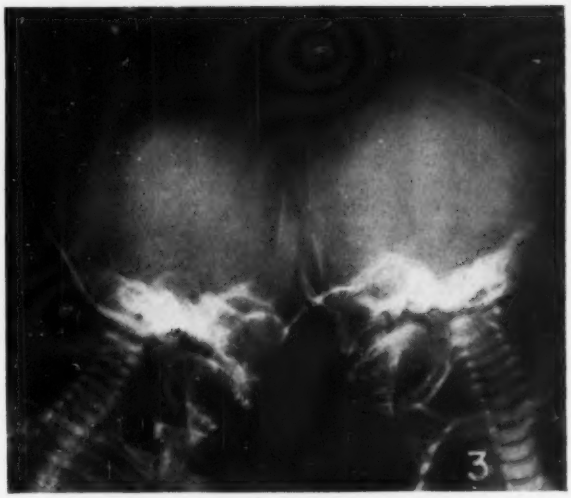

FIG. 3.—Lateral skull radiograph (Tresea is on the left); slight telescoping of the frontal region into the head of Virginia (right) can be noted.

FIG. 4.—Oblique skull radiograph (Virginia is on the left).

The swallowing mechanism, as well as the size, shape, and movements of the tongue were normal. The muscle tone was normal for her age. She showed vigorous movements of all four extremities in all joints spontaneously and as a withdrawal reflex to nociceptive stimuli. There was no evidence of tremors or of abnormal involuntary movements. The tendon reflexes were all present and equal and the plantars were mainly flexor. The abdominal reflexes were present and equal. The sucking and Moro reflexes were well developed. Hand and toe grasp reactions on both sides were equal. She was able to retain very briefly a toy inserted in either hand and her hands were predominantly open.

Laboratory Tests.—The blood group was 0, Rh positive. Haemoglobin was 11·4 g. The urine was normal (CO_2 content 27 mEq./l., serum chlorides 100·2 mEq./l., calcium 9·4 mEq./l., potassium 5·2 mEq./l., and sodium 139 mEq./l.). Radiological examination showed clear lungs, and a normal position and size of the heart and

liver. There were no abnormalities in the skeletal structures. The description of the skull radiographs is similar to that of Virginia (Figs. 3 and 4).

Clinical Diagnosis.—This was cephalopagus frontalis with firm bony union of 24 cm. in circumference. The brains were considered as probably separate, and the dura between the two corresponding parts of the brain was thought to be either absent, the two leaves fused, or separate. The possibility of the blood vessels crossing from one brain to the other was entertained.

It was difficult to care for the infants. Also they seemed to be in apparent discomfort when lifted to an upright position. The sleep of one twin was frequently interfered with by the crying of the other twin. Clearly, their normal development would have suffered if they were left joined for a longer time. Also, any infection in one of the twins would lead to serious consequences for both of them. For these reasons early surgical separation appeared to be the only logical solution. Following detailed consideration of all available data, it was decided that a surgical attempt should be made without preliminary exhaustive tests, such as ventriculograms and arteriograms, in order to avoid any possible complications of delay in separating them.

Operative Procedures.—With the assumption that surgical interference should be minimal, it was decided that the separation would be attempted in two stages and that these operations would not include plastic procedures designed to provide " scalp flaps " to cover the exposed areas of both brains.

The first-stage operation was performed when the twins were 3 months old, on November 9, 1956. After the skin incision over one-half of the junction, the rongeurs were used to separate the bony union. After the dura was incised, a portion of the underlying cortex was exposed. This consisted of small, narrow gyri and moderately deep sulci laced with fine blood vessels. The pia arachnoid overlying the cortex of both twins seemed continuous. After the usual haemostasis, the dura and skin were closed in layers. The common wound was dressed and the patients returned to the ward in good condition. The post-operative course was benign and stable throughout.

The general condition of both infants was good. Their total weight was 7·7 kg. When held in the arms in an upright position at 4 months of age their joined heads were stable and their backs were fairly straight. Virginia was slightly bigger and stronger than Tresea. She followed objects with her eyes and attempted head turning. Her hands were open and she grasped a toy with either hand and shook it vigorously. Tresea was, in general, slightly less vigorous although alert and following the surroundings with her eyes. She also grasped and moved toys with either hand and retained them for several minutes.

The second stage of the operation was performed on December 11, 1956. The twins were postured on dual tables with positions reversed, so that the previous surgical wound was underneath. The anaesthetic was administered by individual endotracheal tubes connected to the same machine. The main aim of this operation was to separate the twins and cover the resultant dural, bony, and skin defects. The separation was relatively uneventful. The skin was incised and retracted. The underlying bone was rongeured away along the exposed circumference so as to leave a channel approximately 2 cm. in width. The exposed dura was then incised and carefully retracted on stay sutures. Next, the cortex was examined for a division. At first none was apparent. However, a close examination of the sulci revealed that one appeared deeper than the others. Further exploration showed that this was, in fact, the surface marking of a dividing fissure. This fissure was fused by a dense pia arachnoid bridge which required both sharp and blunt dissection. Approximately 4 cm. in its depth the frontal lobes were fused directly by means of a fasciculus of white matter 2 cm. in diameter. This bundle contained a lacy network of anastomosing vessels, one of which, an artery, had to be severed during the course of separation. Otherwise there was no need for any major circulatory interruption.

Once the brains were separated, the previous surgical wound was reopened from its inside and the twins lay separate on the tables. In accordance with our previous plan, the large wound defects were covered with reconstituted human dura and skin. (This tissue was supplied by the Tissue Bank of the U.S. Naval Medical Center after being prepared according to their technique.) We anticipated that the dural grafts might " take " but that the skin overlying them would almost certainly slough off. Nevertheless, the skin would provide a temporary covering. This somewhat unusual approach was adopted in order to decrease the risk resulting from many surgical operations. Obviously, the more orthodox plan would call for plastic procedures and thus additional surgery. The wounds were dressed and the patients returned to the ward in good condition. The post-operative course of each twin was not remarkable. For the first two weeks the wounds were dressed each day with bacitracin-saturated gauze. During this short period the skin grafts degenerated and the dural sheets became adherent to the surrounding dura of the infants. There was a considerable leakage of cerebrospinal fluid from the wound of each infant and Virginia developed Friedländer's bacillus meningitis. This infection cleared within three days on energetic treatment with antibiotics administered systemically and locally. After a month the dural grafts were observed to be sealing at their edges. Close examination revealed the presence of fine blood vessels at the junction and their radial growth towards the centre. At the beginning of the sixth month after separation of the twins, the dura was covered with four separate applications of calf embryo skin according to the technique developed by Sylvetti at the Tissue Bank of the U.S. Naval Medical Center. These skin grafts finally resulted in completely covering the external surface of the dura mater. At the age of 1 year the surface of the primary wound was completely epithelialized.

Examination of Twins at 6 Months of Age

Virginia.—Her general state of nourishment was satisfactory. Most of the dural graft had taken and the remainder of the operative area was granulating. Her

weight was 4·6 kg., length 61 cm. She moved spontaneously and to nociceptive stimuli all the extremities, although the left extremities slightly less well than the right. Her tongue slightly deviated to the left and the left corner of the mouth was slightly lower. She had bilateral esotropia but the remainder of the cranial nerves were normal. The tendon reflexes on the left were brisker than on the right. Both plantars were predominantly flexor. On developmental examination her language and motor performance were at the level of 5 months of age. Her adaptive and personal-social behaviour was at the 6 months level.

Tresea.—The general state of nourishment was good. Her weight was 4·8 kg., length 61·1 cm. The dural graft had partially taken but an area about 4 cm. in diameter had to be left for granulation. She moved all her extremities spontaneously and in response to nociceptive stimuli. There was no evidence of focal weakness. Her vision, hearing, and fundi were normal but she had bilateral esotropia. All tendon reflexes were present and equal. On most occasions the big toes were flexor to plantar stimulation. On developmental examination her language and motor performance corresponded to the age level of 5 to 6 months. Her adaptive and personal-social behaviour was at the level of 6 months.

FIG. 5.—The separated babies are 9 months old. They appear healthy and playful. Both have a small dressing over the right frontal region. Tresea is on the left; Virginia is on the right.

Examination of Twins at 9 Months of Age

Virginia.—Her general condition and state of nourishment were good. Her weight was 6·3 kg., length 65 cm. Only a small area of the operative site had not yet epithelialized. There was no demonstrable weakness of extremities although she used her left hand less skilfully than the right and the movements of the left fingers were less elaborate. There was still slight deviation of the tongue to the left and the left biceps and knee reflexes were slightly more active than the right. Both plantars were flexor. Language corresponded to the 8-month level and motor, adaptive, and personal-social behaviour to the 8 to 9 months level.

Tresea.—Her state of nourishment and general condition were normal. Her weight was 6·3 kg., length 64 cm. A considerable portion of the skin grafts had taken although there was still an area of about 4 cm. in diameter which was not epithelialized. She used her extremities equally well on both sides and apart from persisting bilateral esotropia there were no neurological abnormalities. Her language corresponded to the level of 8 months. Her motor performance was at the 9-month level. Adaptive and personal-social behaviour was at the level of 8 to 9 months.

Examination of Twins at 1 Year of Age

Virginia.—The state of nourishment and general condition were good. Her weight was 7·5 kg., length 70·5 cm. The skin over the operative site was completely epithelialized. The head circumference was 38·5 cm., chest circumference was 42·5 cm. Vision, peripheral vision, fundi, and hearing were normal. Her tongue moved in the midline and the remainder of the cranial nerves were normal except for persistent bilateral esotropia. The muscle tone and power were normal for her age and symmetrical. The movements of the left fingers were still slightly less elaborate and less skilful than the right, even if dominance is taken into account. There was no deficit in sensory perception or cerebellar coordination. All tendon reflexes were present and equal and the plantars were flexor on both sides. She was able to stand without support and to take a few steps alone. Her speech was that of 10 to 11 months. Her motor, adaptive, and personal-social behaviour were at the 12-month level.

Tresea.—Her general condition was good. Her weight was 7·3 kg. and length 70·1 cm. The skin defect over the operative area was completely epithelialized. Her head circumference was 38·5 cm., chest circumference 41·0 cm. Her vision, fundi, and hearing were normal. The remainder of the cranial nerves were normal except for the persistent bilateral esotropia. Skill of movements was good in all extremities. She perceived well sensory stimuli and there was no evidence of cerebellar incoordination. All tendon reflexes were present and equal and the plantars were flexor on both sides. She was able to stand without support for a few minutes and to walk a few steps alone. Speech corresponded to the level of 11 months, and motor, adaptive, and personal-social behaviour to the 12-month level.

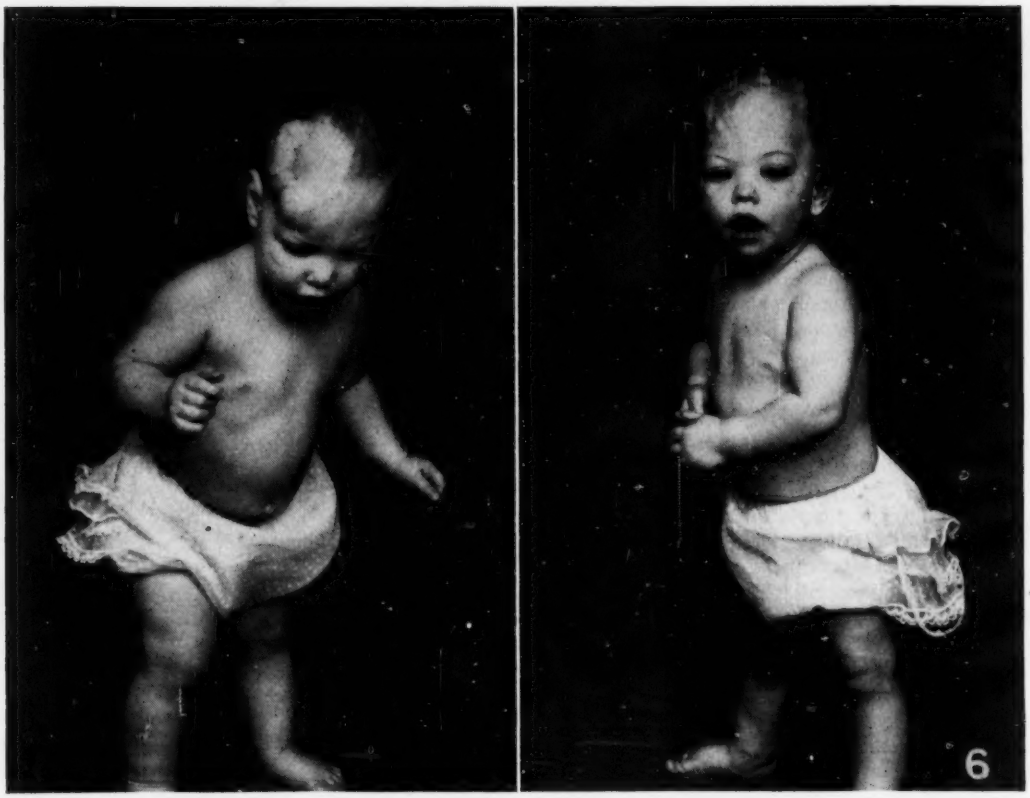

FIG. 6.—The babies are 1 year old. They can take several steps unaided and vocalize a few words. Virginia is on the left; Tresea is on the right.

Discussion

Most of the reports on Siamese twins joined by their heads relate to stillbirths or to viable infants surviving but a short time (Blumensaat, 1932; Mortimer and Kirshbaum, 1942; Gunter, 1946; Coulton, Hertig, and Long, 1947; Leinzinger and Scherrer, 1953; Haug and Leonhardt, 1955, and others).

The known instances when surgical separation of cephalopagous was attempted are only few. In 1928, Cameron described twin infants joined by the whole extent of the vertex of the skull. On the twelfth day of life an attempt at surgical separation was forced by the very rapid deterioration of one twin. Unfortunately, both twins died early in the course of the operation. Leiter (1932) reported cephalopagous twins in whom surgical separation was performed on the eighth day of life by sacrificing one of the twins. However, the other infant also died. Barbosa (1949) published a report on surgical separation of cephalopagous twins. One of the conjoined infants had associated other malformations, hypospadiasis and imperforate anus. The twins withstood the surgical separation but they both died three hours later. Robertson (1953) described a pair of twins conjoined by their heads. After a variety of tests, which included pneumoencephalography and arteriography, surgical separation was attempted but could not be completed because of the rapidly deteriorating condition of both infants. They both died at the age of 8 months, five months after surgical exploration. In 1953, Grossman, Sugar, Greeley, and Sadove reported on surgical separation of cephalopagous male twins. Since this was the first instance of a successful operative separation of cephalopagous twins it warrants more detailed description. Before the operation pneumoencephalography, arteriography, and sinography were carried out. After the skin grafts were prepared the first stage of the operation was performed at 10 months of age. This was followed by complete separation of the twins at 11 months of age. The brains were separate but the tributary veins drained to common dural sagittal sinuses, of which there appeared to be three. These sinuses were left with one twin and the tributary veins of the other twin were ligated. The latter twin died one month after the operation. His twin survives although his mental development seems retarded.

While our report was in preparation, Voris,

Slaughter, Christian, and Cayia (1957) reported another successful separation of Siamese twins joined by the vertex. The dura mater was found to be present between the two conjoined heads. One of the twins developed a marked cerebral hernia and associated left hemiparesis; at the age of 28 months she could sit up alone and say a few words. The other twin talked well at 28 months of age and her progress was said to be satisfactory.

The disturbed morphogenesis leading to conjoined twins presents many interesting problems, most of which, however, cannot be answered definitely at the present time. Excessive speculation would probably obscure more than clarify the issue. The cause of this abnormality in humans is unknown. A few relevant experimental data will be referred to later. In so far as the early embryology is concerned certain information is available. As a starting point and also to provide the basis for discussion, one aspect already raised by the early embryologists needs to be stressed: the mechanism of the production of conjoined twins must be closely related to the mechanism of the formation of uniovular twinning.

Theoretically, uniovular twinning may occur during the following stages of development:

(1) Before or during the early morula stage (first few days after fertilization). This must be extremely rare if it does occur at all. Each of the twin embryos would have to be enveloped in separate chorion and amnion.

(2) During the stage of inner cell mass (blastocyst), approximately seven to 11 days of gestation. Monovular twinning occurs most frequently at this stage. The twins have a common chorion but separate amnions.

(3) During the stage of primitive ectoderm (less than 14 days of gestation), the twins would possess one common chorion and one common amnion. Such twins do occur, although very infrequently.

A conjoined pair of uniovular twins may be either the result of incomplete separation of the formative material or the result of subsequent fusion of once separate embryos. The former possibility will be considered first. It would follow from the above brief outline that if the twinning takes place at the inner cell mass stage and if the separation is complete, the circumstance marking the twinning stage is the presence of a common chorion but two separate amnions. At the inner cell mass stage all cells are pluripotential and after they become separated into two groups normal differentiation will follow in both of them. If the separation is not complete at one locus, development of two embryos will proceed but the tissue which develops from the unseparated cells will remain in junction in a symmetrical fashion.

If the twinning takes place at the stage of primitive ectoderm the mechanism is more complicated. It has been postulated that there exist two or more separate body organizers. Normally one gains complete control and the others are suppressed and finally disappear; in such an instance one embryo results. When, for some reason both organizers continue to be active, two primitive streaks develop and twin embryos result. It is easy to see that there may be a territory in which formative cells are under equal influence of both organizers. In such a case this region will be common to both twins and the joined parts will be symmetrical. The twins will be enveloped by one chorion and one amnion. It is well known (Coulton *et al.*, 1947) that monoamniotic twins are frequently stillborn as a result of compression of the severely intertwined umbilical cords which lead to obstruction of the blood circulation. The possibility of the occurrence of conjoined twins as a result of subsequent fusion of the once separate embryos seems very remote, at least in symmetrical Siamese twins. In the first place the junction would be frequently haphazard and not of the mirror image type, as seen in the majority of cases. Secondly, contrary to the general findings, such abnormality could occur only in monoamniotic twins not separated by the intervening membranes. The experimental work of Mangold (1920) is of considerable interest. This investigator produced conjoined individuals in the salamander by pressing two zygotes together. Since this was a highly artificial situation and concerned achorionic and anamniotic animals it could hardly be applicable to humans or even lower mammals.

In general then, the most likely stage of development when symmetrical conjoined twins are formed is the period of inner cell mass; the probable mechanism is incomplete separation of formative cell material. The cause, both of twinning and of incomplete separation, is unknown. The experimental evidence points to the important role of various factors capable of delaying the process of differentiation at the critical stage (Stockard, 1921). In man, an aged ovum and an abnormal state of the oestrogenic hormone have been suggested, but any objective evidence is lacking.

Development of the Twins after Separation

The development of both our twins following their separation has been surprisingly good. They certainly had many handicaps, such as restricted activity and less chance than normal infants for contact with their environment, until they were

separated at the age of 4 months. Then a long period of about four months of complete confinement first in isolates, then in cribs, when the operative wounds were in a dangerous state with leakage of the cerebrospinal fluid. It was not until they were 11 months old that the operative sites in the frontal regions were completely epithelialized. At the age of 1 year their general and mental development can be considered as being within the normal range. Tresea has been free of any abnormal neurological findings. Virginia shows a minimal decrease in skilled movements of the left hand but power is normal.

Summary

Siamese twins conjoined by their heads are rare. This malformation requires surgical separation if the patients are to survive beyond the stage of infancy. A detailed description of cephalopagous twins is given. The infants were born by natural means and were normal in all respects except for union of the heads. Their development and neurological status before the final surgical separation at the age of 4 months and during their subsequent course is described. Homeo- and hetero- grafts were used to cover the defect of soft tissue at the site of separation. Development of the infants at 1 year of age was normal.

The pathogenesis of Siamese twins is discussed in some detail.

Our thanks are due to the neurological and neurosurgical residents and nursing staff who cared for both patients. In addition we wish to express our appreciation for their generous help to Dr. Thomas Cone, chief pediatrician at the National Naval Medical Center, and to the tissue bank, National Naval Medical School. Details of the anaesthesia were described by Dr. Hall in a separate publication (1957). Miss S. Lewis, R.N., designed a dual table which considerably aided the surgical procedure.

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YAWNING

BY

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Halfway between a reflex and an expressive movement yawning is a very commonplace phenomenon.

Perhaps this is the reason why one searches in vain for a paper on this subject in text-books of contemporary physiology or psychology and that one must be content with the brief definition in the dictionary that "yawning is a deep inspiration made voluntarily with a wide open mouth".

Many authors since Hippocrates, who seems himself to have been interested in the question, have studied either certain aspects or the whole problem. An excellent historical survey of the past knowledge about yawning may be found in the thesis of Trautmann (1901), where are reported the opinions of Galen, Oribase, Sanctorius, Fernel (1610), Kruger (1627), Sennert (1666), Boerhave (1680), Gartner (1736), Albertini (1737), Gunz (1738), Czerniewski (1749), Buchner (1758), Roederer (1759) Haller (1766), Walther (1775) Double (1817), Adelon (1821), Rothmund (1824), Richerand (1825), Muller (1851), Monneret (1861), Longet (1868), and Dechambre and Charcot.

In the twentieth century more papers have been written, among others by Hauptmann (1920), Dumpert (1921), Mayer (1921), Insabato (1928), Peiper (1932), Moore (1942), and Salmon (1948). Two good critical reviews are those by Heusner (1946) and Boudouresques (1950).

The zoologists have not remained indifferent, and they teach us that yawning may be observed in the primates and the carnivores. It is often accompanied by stretching. It is not observed in herbivores. It is difficult to specify its significance, and the connexion between yawning and the movement of opening the mouth that may be observed in fishes, reptiles, and amphibians. The same may be said of the movements made by the bird's beak accompanied by flapping of the wings. Therefore our study shall remain limited to man.

Analysis of Yawning

Yawning is an involuntary, paroxysmal breathing movement. It is a motion unfolding itself in a certain order, wherein three phases may invariably be distinguished : the first one is active and inspiratory; the second phase corresponds to the acme; the third is passive and expiratory. Their respective duration is about 1·5 to 4 sec. each. An average yawn lasts from 4 to 7 sec.

An analysis of the subject's movements may be made by a clinical survey or by the study of radiographs taken every half second, as we have done at St. Antoine Hospital with Dr. Chalut.

In the first phase we see the progressive opening of the mouth, the dilatation of the pharyngo-larynx and of the thorax, and the lowering of the diaphragm. The opening of the mouth is very slow, and the mouth is still half open when the dilatation of the pharynx and the larynx is already at its maximum.

The lowering of the neck's air axis is obvious from simple inspection, which shows the lowering of the thyroid cartilage. A radiograph shows that the body of hyoid bone, which stands at rest at the level of C.2-3 vertebrae goes down to C.6-7, and explains the tongue's situation as it is pulled backward and downward, the tip going well away from the teeth. The dilatation of the glottis and the abduction of the vocal cords can be verified by a laryngoscopic examination sufficiently long continued to catch a spontaneous yawn. The radiographs have shown that the dilatation of the pharynx is enormous and surprising, for it increases to three or four times its normal size (Fig. 1 and 2). The pharynx, larynx, and trachea, as well as the bronchial tubes, appear very dilated on the plates. While the opening of the mouth and the deep inspiration may be observed in many cases apart from yawning, the enormous expansion of the pharynx with the lowering of the hyoid bone and of the tongue is peculiar to yawning.

It is to be noted that the inspiratory sound observed in yawning is produced in the palate and the throat's isthmus. It is not a glottal noise, the glottis being dilated to its utmost at this phase.

The second phase of yawning corresponds to the acme of the mouth's opening and to that of the pharyngeal and thoracic dilatation. Certain pre-

FIGS. 1 and 2.—Radiographs of the pharynx before and during yawning.

disposed subjects may even at this point dislocate the jaw. At this moment appear the facial modifications which began at the end of the first phase. Contraction of the lip dilators exaggerates the mouth's opening and contraction of the eyelids causes a partial or even a total occlusion of the eyes. The nostrils are dilated. The skin at the base of the nose wrinkles and the eyebrows are lifted. At this phase there may also be a degree of tonic contraction of the extensor muscles of the neck and of the trunk, and may extend to include hyperextension of the limbs. The stretching, which is far from constant, has the result of increasing the thoracic capacity. Tears may be secreted, and less frequently saliva.

The third phase is passive. The inspiration ceases abruptly. Expiration is slow and noisy, followed by the sound " aah " originated by the larynx. The pharynx goes back to its normal size, the mouth closes itself, and the face resumes its usual aspect.

This group of complex and synergic motions constitutes yawning. However, yawning may be accompanied by other motions emphasizing or minimizing its action. Yawning may be exaggerated and emphasized by stretching of the limbs, or by a modulation of breathing, or by the execution of rhythmic lateral motions of the mandibles.

Yawning can also be repressed to a certain extent in circumstances where it would constitute bad behaviour; the subject puts his hand before his mouth. He can also repress a yawn by stopping the mouth's opening and controlling the inspiratory motion. But, in spite of efforts, yawning is often betrayed by such a gesture, and a stifled yawn does not escape a careful observer. In this case yawning may be reduced to the action of the pharynx, which once more shows the importance of this phase.

Certain physiological observations have been made during yawning, but they offer small reward. There may be a slight acceleration of the heart in the inspiratory phase with a fall in the index of capillary oscillations in the finger tips. This phenomenon is of no great importance, as it may also be observed during deep inspiration (Heusner, 1946). An E.E.G., if performed in the act of yawning, cannot be interpreted owing to interference by movements and muscle action.

It is noteworthy that a yawn is rarely isolated. It usually occurs in fits of two or three. The intensity of the yawn often increases, and each yawn is separated by a few regular breaths. Sometimes, the yawns will be repeated, irregularly, during several minutes.

Yawning and Stretching

These two actions are often but not always associated. Stretching is connected with the second phase of yawning. Infants and animals stretch and yawn often at the same moment. In adults, stretching is usually observed in the period of awakening. The association of these two motions is far from constant. Yawning, even excluding cases where stretching is repressed by good manners, is often isolated. Likewise, stretching after a long period in the same position is not accompanied by a yawn. These facts allow us not to give quite the same physiological

interpretation to these motions, especially as we shall see in the case of their functional value.

The Cause of the Yawn

There are numerous causes, which may be classified in three categories, physiological, pathological, and experimental.

Physiological.—Drowsiness must be mentioned first: men and animals yawn when they are sleepy. They yawn also when they emerge from sleep. Some persons are subject to yawning and stretching when they awake.

Boredom is a frequent cause. It can be the consequence of different circumstances—a dull talk, a tedious lecture, a wearisome book. Weariness is intimately connected with a lack of interest fundamental to the genesis of yawning.

Seeing others yawning is infectious. " Interdum tamen sola imaginatio ossitationis causa est. Cum enim qui videt alium oscitare, ipse quoque ad oscitandum invitatur " quoted Sennert in 1666. " One yawn brings seven," is a popular saying.

It is easy to make oneself yawn. Four or five deep inhalations with a wide open mouth, imitating spontaneous yawning, provoke yawning. Once the spontaneous yawn has begun, it will seldom remain isolated, and during the following quarter of an hour will be followed by new isolated yawns or by a fit of yawning.

Hunger or, the contrary, the plenitude after a heavy meal, are generally admitted as inducing yawning. In the second case yawning is associated with drowsiness. Certain plethoric patients seek medical advice for these post-prandial yawns.

Yawning is frequent in certain circumstances, such as physical weariness or pregnancy.

Pathological.—Yawning is commonly observed in lesions of the brain-stem. It can also be seen in intrinsic lesions (haemorrhage, softening, tumours), and in compressions (posterior fossa tumours). It is noteworthy to recall that drowsiness is a symptom of peduncular softening (Lhermitte).

If yawning is commonly observed in hemispheric tumours, especially frontal and temporal tumours, and in hemispheric haemorrhage, it is probably due to indirect compression of the brain-stem provoked by intracranial hypertension or a temporal herniation. In such cases a yawn serves as an indication of a brain-stem lesion and bears a bad prognosis.

In the course of diffuse lesions of the brain, yawning is not infrequent. It has been observed in cases of alcoholic encephalopathy and of general paralysis of the insane.

Yawning is frequent in respiratory sequelae to encephalitis lethargica, together with sighs and spasmodic hiccup. Sicard and Paraf (1921) and Turner and Critchley (1925) mention spasmodic yawning and gaping. Choreics also yawn. Yawning can be observed in certain varieties of epilepsy. Wilson (1940) interprets yawning as an " aura " of visceral crisis.

Penfield and Jasper (1954) mention two observations of yawning as an element of autonomic diencephalic seizures. They cite the case of a woman of 29 with a large astrocytoma occupying the whole left temporal lobe and the lower portion of the corpus striatum, whose fits started abruptly with occipital pain accompanied by yawns and hiccups while at the same moment the left arm and the left side of the mouth became numb. The fit ended with a need to urinate.

Yawning has been described very often and with many details as a manifestation of hysteria (Charcot, Dejerine).

Salmon (1948) points out that fits of yawning may be a sign in myasthenia gravis and quotes one of his personal cases and one of Albertoni's. He indicates the action of prostigmine in stopping yawning. Yawning is also noted in the course of anaemia, haemorrhage, and shock, and during pyrexia, as well as in digestive disturbances, though no one has tried to explain its mechanism in this case.

Yawning and Cerebral Stimulation.—A comparison is possible between the natural causes of yawning and yawning created experimentally by intracerebral stimulation, but we do not know of any research work. On the other hand, yawning has been studied and noted in certain protocols. Hess (1938), by stimulating the intralaminar substance of the thalamus and the posterior subthalamus, has induced sleep in cats after fits of yawning. The experiments of Passouant, Passouant-Fontaine, and Cadilhac (1956) on the stimulation of the rhinencephalon, and particularly of Ammon's horn, also mention yawning. The induced crisis has three phases: during stimulation, reaction of escape, and during the post-discharge period, uneasiness with a diminution of watchfulness. In the third phase the animal stands, licks itself, purrs. This manifestation of well-being lasts a few minutes, and sometimes the animal lies down, stretches, yawns and goes to sleep.

Sleep may start three or four minutes after the discharge. An E.E.G. of the hippocampus shows that it is preceded by sharp waves with increased voltage.

It is obvious in this case that yawning is only a late and indirect manifestation of stimulation. We must remember, however, that it is integrated in a behaviour of well-being and sleepiness opposed to the reaction of escape simultaneous with stimulation.

The fact that yawning may be observed during the stimulation of the rhinocephalon or hypothalamus, formations which are functionally and intimately joined with the reticular activating system, must be emphasized.

Linked Yawning and Stretching.—In normal subjects yawning and stretching may be independent of one another, but in some pathological conditions they are tightly linked. Dumpert (1921) and Lewy (1921) refer to the clinical observation of hemiplegic patients in whom yawning was attended by stretching the paralysed arm. Heusner (1946) also mentions spontaneous stretching of the paralytic arm provoked by a yawn.

Physiology of Yawning

While the clinical aspects and the determining causes of yawning are well known, its physiological mechanism is no better known than its significance.

Besides the fanciful interpretations already mentioned, a certain number of theories have been brought forward that may be classified in two groups according to whether the yawn is a secondary or a primary disturbance.

In the first group yawning is considered as a mechanism of regulation, just as shivering is considered as an automatic reaction opposed to the cooling of the organism. No agreement has been reached, however, either on the nature or on the mechanism of this regulation.

Hauptmann (1920) suggested that yawning and stretching were opposed to muscular hypotonia which, like boredom, is the consequence of the inactivity of superior brain centres. Salmon (1948) maintains that yawning is an automatic reaction of the respiratory muscles caused by hypotonia of the respiratory bulbar nerves and by the hypotonia that follows sleep. But Dumpert (1921) went farther in this hypothesis. He considers that yawning occurs when the brain circulation is not sufficient to maintain wakefulness and vigilance. Yawning and stretching should increase venous circulation to the heart first by compressing the veins of the trunk and the limbs as well as the splanchnic veins; secondly, by diminishing the intrathoracic pressure. The resulting venous hypertension increases the cardiac output (Bainbridge's reflex) and consequently improves arterial irrigation. The brain circulation benefits especially, and, further, the sensory stimuli from the stretched muscles produces, according to Dumpert, systemic vasoconstriction and vasodilatation of cerebral arteries. Stretching, and to a lesser degree yawning, might thus produce an increase of blood circulation sufficient for the maintenance of wakefulness.

Among the functional theories of yawning, the hypothesis quoted by Heusner (1946) of a secretion of thyroxin determined mechanically by the compression of the thyroid gland during yawning should be mentioned.

Beside these resolutely finalist theories, some authors neglect the physiological consequences of yawning and consider it as an accident connected with cerebral strain (Mayer 1921), just as crying and laughing are the expressions of pain or joy.

For Peiper (1932), yawning is a transitory disorder of the respiratory centres, weariness producing a decrease of the excitability of the superior respiratory centres liberating an underlying centre for yawning.

These theories, without being completely opposed, are based on unverified or disproved physiological hypotheses, such as the increase of venous pressure during yawning or the decrease of the cerebral blood flow when wakefulness ceases. They still leave unexplained certain aspects of the psychomotor reflex described as yawning.

In the light of contemporary knowledge of psychophysiology, it is possible to attempt an explanation of the mechanism of yawning, while nevertheless underlining the gaps open to further research.

The Mechanism of Yawning

Yawning is a complex, involuntary, and paroxysmal act. Under the influence of a certain number of facts, a brief (4 sec. to 7 sec.) motor activity takes place, bringing into play a great number of thoraco-cervico-facial muscles. This suggests a critical activity spreading from one place to another in a given neuronal circuit. With the knowledge of the muscles participating in yawning, it is possible to state that the motor nuclei involved are located in the bulb and in the cervical cord. It is therefore possible to state that yawning, or more exactly the motion of the yawn, is connected with a paroxysmal discharge involving a certain number of motor nuclei situated in the bulb and in the cervical cord. The extension of this discharge to the nuclei of the trunk and the limb muscles induces stretching.

It seems impossible to specify whether there exists a hierarchy in this neuronal structure which would allow us to locate a " centre of yawning ". But, on the other hand, we may note that this structure has a close relationship to both the reticular formation and the cerebral cortex. The brain-stem reticular formation appears, according to a large number of studies of Magoun (1950) and of Moruzzi and Magoun (1949), to be capable of modifying the central excitatory state, and thus of controlling the degree of alertness. It determines the level of consciousness in its arousal capacities, alertness declining

in sleep and in pathological states related to sleep (drowsiness, torpor), and disappearing only in deep coma, and, on the contrary, increasing in varying degrees according to the intensity of stimulation and, probably, to the extent of the nervous mechanism set in motion.

Participation of the cerebral cortex cannot be contested when yawning is the result of complex psychic activities such as imitation or boredom. It is interesting to recall in this connexion the experiences of French, Hernandez-Peon, and Livingston (1955) showing that efferent pathways issuing from the cerebral cortex appear to project down to the reticular formation.

If we maintain this hypothesis, which should be verified, particularly by recording the neuronal activity of the nuclei set in motion by yawning with intrabulbar electrodes, the standard E.E.G. being uninformative, we must answer the following question: Which are the responsible factors in the paroxysmal discharge in this bulbo-medullary motor structure ?

Circulatory and Humoral Factors.—These must first be discussed because they have generally been invoked though without any accurate experimental data.

The frequency of the yawn in the course of anaemia or circulatory insufficiencies invokes the possibility of bulbar anoxia or modification of the CO_2/O_2 ratio. We lack precise facts on this subject, but we can observe that voluntary apnoea, even if it lasts some time, does not cause yawning. There is no proof that a slight variation of bulbar circulation will carry with it anoxia. On the contrary, we know the part played by Hering's nerve and the carotid sinus in the regulation of cerebral circulation as well as the constancy of this circulation under physiological conditions. Furthermore, one does not observe yawning when the central cerebral circulation is insufficient, as in the paroxysmal fits of bradycardia in the course of the Stokes-Adams syndrome.

Some authors also mention the part taken by humoral modifications. Yawning and post-prandial drowsiness may be attributed to an alkalotic wave or a discharge into the blood of polypeptids or lipids of digestive origin. It could also be produced by intermediary metabolites due to muscular strain. Crämer (1924), noting the frequency of yawning in patients with colitis, assumed that it was due to an auto-intoxication by bacteriological toxins produced in the bowel. In fact, the existence of an endogenous origin has not been proved any more than that of an endogenous hypnotic substance.

Pharmacology provides, on the contrary, drugs predisposing to the appearance of yawning and of drowsiness, as is the case with morphine and hypnotics. The action of these substances on the reticular formation is well known, whereas caffeine and amphetamine have an opposite effect. In conclusion, if yawning can be induced by pharmacological means, there is no formal proof of the part taken by circulatory or humoral disturbances in the genesis of yawning.

It must be noted that if such disturbances exist, which remains possible and must be the subject of further studies, they could only be an adjuvant cause, their duration clearly exceeding the duration of yawning, which may or may not appear in instances such as after meals, according to the psychological condition of the subject.

Psycho-sensorial Factors.—Spontaneous yawning must be distinguished from yawning by imitation. Both are influenced by the surrounding circumstances, but in different ways.

Spontaneous yawning occurs in particular physiological circumstances such as weariness or sleepiness. In these cases, the subject lacks interest in his surroundings and spontaneous thought diminishes. On the contrary, one does not yawn and even if one is drowsy, one awakes if a new stimulus abruptly appears. It may be physical stimulation or affective shock which rouses attention. People do not yawn at the very moment they learn the result of an important examination or the news of an accident to a relative. Yawning only occurs in psychological conditions of indifference or lack of interest in surroundings.

Knowing the part played by the reticular formation in the mechanism of wakefulness, we propose the following hypothesis. Yawning is an integrated discharge in a bulbo-reticular motor structure occurring at a particular level of activity of the reticular formation corresponding to a decrease of wakefulness preceding sleep. This hypothesis, which is in agreement with neurophysiological and pharmacological principles, explains why yawning may be observed when a subject begins to sleep as well as when he awakens. In our opinion, yawning appears as a physical manifestation of a drop in wakefulness. This paroxysmal motor discharge may be compared with the muscular hypotonia observed during sleep. It is the expression of a mode of being and does not constitute a reaction against it. It should not play any physiological part. In fact, yawning, as we know, induces yawning and does not induce wakefulness. Yawning should be distinguished from stretching, which perhaps has the function of setting wakefulness in motion.

Yawning by imitation may occur in certain

circumstances of release of interest, but the fact that it can be induced shows that we maintain a certain degree of consciousness in our surroundings which involves some participation of our system of wakefulness. The infectiousness of yawning is only one example of the numerous acts caused by imitation, often quite unconsciously, for instance, repeating a tune, raising or lowering one's voice according to one's interlocutor, answering a grin by another grin, or a smile by a smile. In the same way, some expressive acts such as laughing or crying are infectious in certain circumstances. There is still much to discover in the mechanism of association. However, the possibility of associating two stimulations, two ways of behaving, two ideas, is at the basis of learning. Infectious yawning is just one particular case in a series of imitative gestures.

It is also difficult to interpret the mechanism which determines a real, spontaneous, irrepressible yawn after a fit of false yawning. The passage of a voluntary act to a paroxysmal and involuntary one is difficult to interpret on purely associative grounds, and one may wonder to what extent the fact of yawning voluntarily, by a mechanism which remains to be described accurately, has not modified neuronal excitability, thus facilitating the paroxysmal and involuntary discharge.

Psycho-social Significance of Yawning.—Let us eliminate from this discussion infectious yawning, an imitative gesture which is proof of a normally suggestible subject and of his psychological irresponsibility, and let us return to spontaneous yawning.

Without any physiological usefulness, spontaneous yawning has still a psychological significance: it shows lack of interest. This psycho-physiological conception carries with it certain considerations on the social circumstances under which yawning occurs.

Yawning has an expressive mimic value as long as it indicates indifference and boredom. The interest or lack of interest that we feel for our surroundings certainly depends on the nature of the surroundings. The interest of the subject will be very differently stirred according to whether he is lying peacefully in silence and in darkness, or whether experiencing sensory or psychic stimulation. This applies to infants as well as to adults. For the latter, however, the interest he feels for the exterior world depends largely on his personality and his former experience. Interest is conditioned by different factors, such as family, school, profession, social position. For instance, a conversation on an unfamiliar topic, or concerning an unknown person, causes lack of interest. The same could be said of a discussion in a foreign language. It is well known that a connoisseur will bore the layman if he speaks at length on an esoteric subject. To a certain extent it is easy to know when the subject will please or bore, one's taste representing exactly what one is interested in. The intimate connexion between interest and personality explains the expressive value of yawning, which appears as the mark of unconcern and disinterest. It may be said that yawning is to boredom what the gestures of laughing and crying are to joy and sorrow.

This interpretation of the significant value of yawning agrees with the popular opinion that yawning is a symptom of boredom. The fact that it is polite to put one's hand before one's mouth when yawning, that is, to hide a yawn, a habit learned in childhood and which becomes automatic to the point of being an integral part of the yawn, is an implicit acknowledgement of the social significance of that motion expressing weariness and refusal, which it is better to dissimulate.

It is possible that in putting forward a digestive trouble as an explanation of yawning the subject unconsciously tries to hide the real cause, boredom. As an involuntary expressive gesture, yawning, is, however, a conscious phenomenon to which, in the course of its automatic development, voluntary modulations may be added. For instance, a suppressed yawn shows an endeavour to dissimulate boredom. On the other hand, an emphasized yawn, long and noisy, proves in an unequivocal manner that the subject wants to show his weariness or even his aggressive attitude to a situation for which he does not feel any interest.

Summary

The different phases of the yawn are described, while the physiological and pathological causes are considered.

The classical theories of yawning are discussed. The following views are put forward:—

(*a*) The yawn is connected with an integrated discharge in a bulbo-cervical motor complex which appears at a certain level of excitability of the consciousness arousal system (reticular brain-stem formation) corresponding to the lessening of alertness preceding sleep.

(*b*) This particular state of alertness depends on sensory stimulations received from the surroundings. It can also be induced experimentally by intracerebral electric stimulation or by certain drugs (hypnotics).

The part played by endogenous factors (circulatory or humoral), though often discussed, has never been proved.

(*c*) On physiological grounds, yawning appears

as the physical manifestation of a lowering of wakefulness, and does not seem to have any physiological function.

(*d*) From the psychological point of view, yawning by imitation may be considered as one particular case in the series of imitative gestures. Spontaneous yawning, on the contrary, may be included among the expressive gestures. Interest as well as lack of interest is intimately connected with the personality. Yawning, which expresses boredom, unconcern, and indifference to certain circumstances, has the value of a refusal, and even in certain cases of an unconsciously or consciously aggressive attitude.

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OPHTHALMIC HERPES ZOSTER WITH CONTRALATERAL HEMIPLEGIA

BY

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Cases of herpes zoster are not rare in everyday medical practice and the various neurological complications, such as post-herpetic neuralgias, are well known. Myelitis or encephalitis, on the other hand, are much rarer complications.

The following case admitted to the Neuropsychiatric Clinic of the University of Salonica is of special interest because of the focal cerebral lesions, which are very rare sequelae of herpes zoster.

A single man, aged 29, a farm worker from Konitsa in northern Greece, was admitted on April 29, 1957. There was nothing significant in his family or previous personal history. He consumed moderate quantities of tobacco and alcohol. He was right-handed.

On March 23, 1957, the patient developed a typical left ophthalmic herpes zoster, with slight ptosis of the left eyelid and diplopia on looking upwards. He recovered from his illness in a few days, and was well, except for slight pain in the left frontal region.

On April 26, while lying in bed, but before falling asleep, all of a sudden he discovered that he could not speak and at the same time that his right arm and leg were weak.

On examination, the skull was normal on palpation, without any bruit. The visual fields were normal. The left pupil was definitely larger than the right and reacted sluggishly to light and on accommodation. There was no nystagmus but slight ptosis of the left upper lid. The lower part of the right face was paralysed and the upper part was slightly affected. The pharyngeal reflex was sluggish and the tongue deviated to the right when protruded.

Voluntary movement in the upper limb was abolished on the right side. There was slight hypotonia on the right. The tendon reflexes were less marked on the right. Meyer's sign was absent on the right. There were no trophic disturbances. The abdominal and cremasteric reflexes were less brisk on the right side. Movements of the lower limbs were not fully performed and power was reduced on the right. The tendon reflexes were brisker on the right. Both plantar reflexes were extensor, more so on the right. Oppenheim's and Rossolimo's signs were present on the right. His gait was hemiplegic. All forms of sensation, including the discriminative, appeared to be normal, as far as could be judged in the presence of aphasia.

The patient did not speak spontaneously and on questioning he could hardly pronounce simple words and then only hesitantly. He could point to various named objects, but could not himself name them. He obeyed simple commands, though sometimes with a degree of perseveration, and understood written phrases, even complicated ones, but could not write even with the left hand.

No apraxia or agnosia was found.

Nothing abnormal was demonstrated in the cardiovascular, respiratory, or other systems.

The cerebrospinal fluid on April 30 was clear at a normal pressure (protein 44 mg. and sugar 60 mg. per 100 ml., 4 lymphocytes, Pandy negative). The blood urea level was 40 mg., and blood sugar 70 mg. per 100 ml. The E.S.R. (Westergren) was 5 mm. in the first hour, 10 mm. in the second hour. The Wassermann and Kahn reactions of blood and C.S.F. were negative.

There were slight traces of protein in the urine. A blood count gave 3,700,000 red cells and 5,400 white cells per c.mm.; Hb 75%. Radiographs of the skull were normal.

The patient's condition gradually but definitely improved, so that a month after the onset of the paralysis power was almost fully restored in the right leg, and less so in the right arm and face. The aphasic disturbances subsided to a great degree, but a slight difficulty in pronouncing unfamiliar words was left. There was slight sensory loss in the left frontal region. The tendon reflexes were brisker on the right and the plantar reflexes still extensor.

The Literature

The case is described above of a patient who, four weeks after the onset of left ophthalmic herpes zoster, presented with a right hemiplegia and expressive aphasia and agraphia. This case is of special interest because of the very great rarity of purely focal lesions in the brain after herpes zoster, in contrast to the generalized involvement of the brain (meningoencephalitis) which is not a very rare complication (Schiff and Brain, 1930; Biggart and Fisher, 1938; Krumholz and Luhan, 1945). Myelitides of various kinds were also described, *e.g.*, the Landry type (Wohlwill, 1924; Schuback, 1930), the Brown-Sequard type (Wilson, 1954), transverse myelitis

(Bruce, 1907), and of course, the post-herpetic lesions of the lower motor neurone and the peripheral sensory pathways are well known (Taylor, 1895; Cornil, 1930; Carter and Dunlop, 1941; Taterka and O'Sullivan, 1943; de Gispert Cruz, 1955; Schwetz, 1955).

Brissaud, for the first time, in 1896, described two cases of hemiplegia following herpes zoster, but in neither was the cause certain. In the one the symptomatology was suggestive of subarachnoid haemorrhage, and in the other the hemiplegia was developed gradually, and the possibility of a cerebral tumour was not excluded.

In 1929 Faure-Beaulieu and Lhermitte described a case of herpes of the eleventh and twelfth dorsal segments with right hemiplegia. This case seems, however, to be rather, as other authors also accept, a case of cerebral thrombosis. A similar case was described by Lhermitte and Vermès (1930): a man of 75, who, three days after the onset of herpes zoster of the second cervical dermatome presented with a right hemiplegia. But this case was complicated by a positive Wassermann reaction and is not considered with certainty as due to the herpes zoster.

We consider the following cases of hemiplegia to be due definitely to herpes zoster.

(1) The case of Dumary in 1896 described by Baudouin and Lantuéjoul in 1919 in which, four weeks after a right ophthalmic zoster a left-sided hemiplegia occurred, without any signs of generalized encephalitis, or other general symptoms.

(2) The case described by Hughes (1951) in which, in a woman of 70, with a right ophthalmic zoster, a left-sided hemiplegia occurred four weeks later.

(3) The case of Cope and Jones (1954) in which, in a woman of 54 and a month after the onset of a right ophthalmic zoster, a left hemiplegia was established in one day.

(4) The case of Gordon and Tucker (1945), in which a man of 26, three weeks after the onset of a left ophthalmic zoster, presented with a paralysis of the right upper limb and face, and on the fourth week with paralysis of the right lower limb in addition. There was also a gross expressive aphasia. This case is the only one we could find in the literature in which aphasia accompanied hemiplegia after herpes zoster.

Discussion

The aphasic disturbances suggest a cortical or subcortical localization of the lesion, and the absence of such aphasic disturbances in three of the cases was evidently due to the right-sided localization of the lesion.

In all five cases of focal lesion of the brain, the herpes involved the ophthalmic branch of the trigeminal nerve and the focal lesion was always in the ipsilateral hemisphere. There can be two possible explanations, either local meningo-encephalitis or arteritis leading to thrombosis.

Though no pathological study was possible in any of the cases, in view of their rapid recovery, the sudden onset without any prodromal symptoms and the rapid recovery in itself are in favour of a vascular lesion. Gordon and Tucker also consider that their case of hemiplegia and aphasia was due to a local haemorrhage or thrombosis; they exclude embolism because in their case, as in ours, no source of an embolus was evident.

Feyrter (1954) described a case of a woman with hypertension and a fatal apoplectic incident, in which histologically a necrotic arteritis of the type of periarteritis nodosa was found in the medulla, cerebellum, cerebrum, and meninges, mainly on the right side. Three months before her death the patient suffered from right-sided ophthalmic zoster with keratitis and iritis. After a thorough post-mortem examination of other parts of the body, mainly the viscera, no signs of arteritis were found and for this reason Feyrter considers the arteritis of the brain to be due to the zoster. Many descriptions of necrotic arteritis in herpes zoster can be found in the literature, but it was not always considered to be due to the herpes zoster. Maybaum and Druss (1934) reported a case of periarteritis nodosa with pain and blebs on the pinna, auricle, and tympanic membrane six weeks before death.

It would be interesting if focal lesions of the brain due to herpes zoster without skin manifestations could be demonstrated. Aitken and Brain (1933) describe several cases of facial palsy without skin eruption, in which the diagnosis of herpes zoster was verified by complement-fixation tests. Feyrter (1954) and Denny-Brown, Adams, and Fitzgerald (1944), on the other hand, say that the sensory ganglia are not always involved in herpes zoster.

Denny-Brown *et al.* found necrotic lesions in the spinal ganglia in cases of spinal herpes zoster. Similar lesions with haemorrhages were described by von Bärensprung as early as 1862 and by Head and Campbell in 1900. Bruce (1907) thought that the spinal lesions in herpes zoster could be accounted for by an inflammatory thrombosis of the postero-lateral or posterior cornual arteries. Denny-Brown's pathological findings were necrotic areas of remnants of cell bodies with zones of inflammation (lymphocytes and plasma cells), and they resembled infarct necrosis suggesting vascular occlusion. Strong evidence in favour of the latter was the finding of an artery of a ganglion actually thrombosed. Cuffing of the vessels and endothelial proliferation was a common finding.

The thrombosis of vessels in herpes zoster, on the other hand, cannot be considered as a sequel of a generalized invasion of the central nervous system by the virus, because in that case the focal lesions would be expected in other parts of the central nervous system as well and not only ipsilaterally. It seems therefore that only a certain region of the brain around the Gasserian ganglion is involved, and that can even be shown in the case of Feyrter where, despite the rather generalized arteritis in the brain, lesions were more marked ipsilaterally to the invaded dermatome.

In contrast to the views of Gordon and Tucker, Cope and Jones accept for these cases of hemiplegia a direct spread of inflammation from the Gasserian ganglion to the corticospinal tract, and they thus try to explain the steady onset of hemiplegia three to four weeks after the onset of the skin eruption.

It may be significant that, in contrast to the usual finding of an increased number of cells in the cerebrospinal fluid, in our case the sample of fluid taken a few days after the onset of the paralysis contained only four cells (confirmed later by another lumbar puncture showing seven cells), and in Gordon and Tucker's case three cells and normal protein were found. This points to the fact that the meninges are not necessarily involved, as should be the case in a direct spread.

We think that there is a ganglionitis with secondary involvement of nearby vessels in the form of an arteritis, needing a certain period of time to lead to thrombosis, and thus the difference in the time of onset of the herpes and the focal symptoms can be explained. If, on the other hand, one accepts that there is simultaneous inflammatory involvement of the vessels, then the formation of a clot in a large cerebral vessel, later driven away and occluding smaller vessels, may be a plausible explanation.

It is noteworthy that focal lesions of the brain are always associated with herpes zoster of the ophthalmic branch of the trigeminal nerve, which is in close relationship to the middle cerebral artery, especially in its first part where the lenticulo-striate arteries arise to enter the anterior perforated substance and supply the internal capsule.

Summary

A case of right-sided hemiplegia with expressive aphasia following left ophthalmic zoster is described. On attempting to review the literature of focal cerebral lesions following herpes zoster, only four such cases could be traced. These all caused hemiplegia (one with aphasia), and all followed herpes zoster of the ophthalmic branch of the trigeminal nerve. Their common findings are discussed and the possible pathogenesis. The view is put forward that the vessels in the neighbourhood of the Gasserian ganglion may be involved in the form of an arteritis, leading to a vascular incident in the ipsilateral hemisphere.

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A PRELIMINARY REPORT ON THE LACK OF TOXICITY OF A PREPARATION OF TOTAL RAUWOLFIA ALKALOIDS

BY

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In disturbed patients with mental illness of many kinds, the benefits of reserpine are well recognized, though in many cases the side-effects are so unpleasant as to outweigh the advantages (Hambling, 1957). Besides reserpine, other Rauwolfia alkaloids are active (Schneider, Plummer, Earl, and Gaunt, 1955); indeed the whole root has been used in India for centuries by Ayurvedic physicians under the popular name of Pagal-ka-deva, or insanity herbs.

It was thought that a preparation containing all these alkaloids might be free from some of the side-effects of reserpine alone, as papaveretum tends to cause fewer side-effects than morphine (Douthwaite, 1957). Such preparations include " raudixin " supplied in tablets containing 50 mg. of the crude root, *i.e.*, about 0·4 mg. of the total alkaloids, and " serpina ", supplied in tablets containing 4 mg. of the total alkaloids.* Kline (1954) used small doses of raudixin and reserpine; apparently he found little difference. Serpina has been investigated in the treatment of hypertension and mental illness, and is said to be relatively free from toxic effect (Vakil, 1949; Klausgraber, 1953; Wilkins, 1953; Wilkins and Judson, 1953). I report here a preliminary clinical investigation in mental patients.

In the first experiment " serpina ", reserpine, and a placebo were given to psychotic patients and the response and side-effects compared.

In the second experiment, in a dose found safe and effective in the first experiment, " serpina " was given to a larger number of patients for a longer period.

First Experiment

Thirty-six chronic psychotic men, all restless and excitable, were divided into three groups (*A*, *B*, and *C*) according to the alphabetical order of surnames, except for some adjustment to ensure that each group contained patients of about the same age. Of the Group *A* patients, 11 were schizophrenic and one epileptic. Of the schizophrenics, four had had leucotomies; one of these four and one other were taking chlorpromazine. Group *B* contained 11 schizophrenics and a paraphrenic; four of the schizophrenics had had leucotomies and one was taking chlorpromazine. Group *C* contained 11 schizophrenics and a manic-depressive; four schizophrenics had had leucotomies; one of these, and one other, were taking chlorpromazine. The chlorpromazine was continued throughout the experiment, in view of the reported adverse effects of sudden withdrawal (Trethowan and Scott, 1955). The groups were well matched (Table I) in age, duration of symptoms, presumed basic intelligence, and behaviour rating on a modified Elgin scale (Wittmann and Russell, 1942). Similar proportions in each group were employed in similar occupations, *e.g.*, kitchen, farm, etc.

The nurses, who did not know which preparation was which, gave drug and placebo according to a

*These include reserpine, reserpinine, ajmaline, ajmalinine, ajmalicine, isoajmaline, neoajmaline, serpentine, serpentinine, sarpagine, rauwolfinine, raupine, corynanthine, isorauhimbine, yohimbine, thebaine, papaverine, and reserpic acid methyl ester.

TABLE I
COMPARABILITY OF THE THREE GROUPS IN FIRST EXPERIMENT

Group	*A*		*B*		*C*	
	Range	Average	Range	Average	Range	Average
Age (yr.)	25–61	38·9	22–61	37·4	22–58	37·1
Duration of symptoms (yr.)	4–33	14·2	2–32	14·9	3–30	14·6
Behaviour rating*	1·5–3·7	2·5	1·8–3·3	2·3	1·9–4·2	2·7
Assumed† basic intelligence	1–4	2·9	1–4	3·0	1–4	2–5

* One deteriorated, five normal.
† One mentally deficient, three average.

TABLE II

DOSAGE OF DRUGS AND PLACEBO IN FIRST EXPERIMENT

Day	Group *A*		Group *B* and *C*	
	Injections	Tablets	Injections	Tablets
1–10	1 ampoule a.m. 1 ampoule p.m.	1 noon	1 ml. a.m. 1 ml. p.m.	1 b.i.d.
11–20	1 ampoule a.m.	1 p.m.	1 ml. a.m.	1 t.i.d.
21–91	Nil	1 a.m.	Nil	2 t.i.d.

fixed time table (Table II). Thus each patient had injections and tablets for 20 days, then tablets only. The nurses also recorded the pulse rate and blood pressure of every patient before injection and an hour after, for the first three days, then weekly; the weight and urine test for sugar (weekly); and behaviour and side-effects.

High doses of the drugs were used. Group *A* patients were given reserpine (5 mg. in each ampoule and 5 mg. in each tablet); Group *B* patients were given injections of sterile water, and " serpina " tablets (4 mg.); and Group *C* patients were given injections of sterile water and placebo tablets.

Results

The nurses could soon tell that Group *A* was receiving an active drug, because of the high incidence of side-effects. Of the 12 patients, pneumonia developed in three, so that treatment had to be interrupted. Ten patients completed the trial; all had side-effects, including drowsiness, shivering, tremors, epileptic fits, increased salivation, and rigidity, stuffiness of the nose and eyes, oedema of the face and feet, sudden falls in blood pressure, dizziness, and fainting, and diarrhoea and vomiting. In some cases these began three hours after the first injection; in others they were delayed for several days.

After about three weeks, improvement in disturbed behaviour began to be obvious in Groups *A* and *B* (Table III). During the second 10 days of

TABLE III

NUMBER OF PATIENTS IMPROVED IN EACH GROUP IN FIRST EXPERIMENT

Degree of Improvement	Group		
	A	*B*	*C*
Much	1	0	1
Moderate	8	8	8
None	1	4	9
Transferred	2	0	0
Total	12	12	12

the experiment, all patients in Group *A* passed through the usual " turbulent " phase; this was not seen in any patient in Group *B* at any stage. Two patients in Group *A* had oedema of the feet while under treatment, but two in Group *B*, who adopted catatonic postures and habitually had oedema of the feet, were relieved of this during treatment.

In Group *C* little improvement was seen (except in a patient taking chlorpromazine), and there were no side-effects. There was no striking change in weight in any group.

Second Experiment

In view of the improvement without side-effects in the patients given the total alkaloid preparation, a further 34 chronic psychotic men were treated with it.

Patients were chosen whose condition had become static and in whom improvement was not expected except through some novel treatment. Their average age was 49 (range 30-67), and they had been in hospital on average for 18 years (range two to 35). They were more disturbed than the patients in the first experiment; all were unemployed and unoccupied, and uninterested in their personal appearance. Ten were wet and dirty by day, and nine had to be told when to use the toilet. Seven had to be washed and dressed. A number of them needed sedation at night, and constant supervision of dress and appearance. One was destructive, tearing up his clothing, and had to eat alone.

Treatment and Response.—Two 4 mg. tablets of " serpina " were given thrice daily, and improvement began to be apparent after about three weeks. The unmanageable patients became manageable, and all but three were employed—some without supervision. Most could sleep in unsupervised dormitories, which had previously been impossible. Eighteen were able to shave themselves; none were wet and dirty, none had to be washed or dressed, and a minimum of toilet supervision was needed. There were no impulsive outbursts; the destructive patient no longer tore his suits, and his table manners had improved so much that he could eat with the other patients.

No patients could be discharged (often because they had been in-patients for years and had no homes), but a few were well enough to be allowed out at week-ends for the first time.

Side-effects.—After 22 weeks' treatment, the blood pressures were not materially different, except that in four patients with mild hypertension the pressure had become normal (190/110 mm. Hg to 130/80, 180/100 to 116/60, 150/100 to 114/78, and 140/100 to 114/68). In three others it fell appreciably (130/80 mm. Hg to 96/70, 125/80 to 90/60, and 114/68 to 80/50); two of these had one dizzy spell each. There were no other side-effects at all in the whole series.

When treatment was stopped after 22 weeks, there was some regression, but the patients had become more amenable to habit training, and have not returned completely to their former condition. A few have been given chlorpromazine with some success.

Discussion

A preparation of total Rauwolfia alkaloids has been found to be as effective as reserpine in a group of disturbed patients, and strikingly free from side-effects in this and in a larger group treated for a longer period. As Kline and Stanley (1955) write:

> " . . . the problem is not solely whether a preparation such as reserpine will cure an individual patient, but whether the over-all therapeutic picture is improved by the addition. Does it act on large numbers of patients more rapidly, more inexpensively, and more permanently than other forms of treatment for specific conditions ? It is necessary to adhere to the dictum of ' the greatest good of the greatest number '."

By these criteria, " serpina " seems to merit a place as a useful drug. More information is needed about the constituent alkaloids, but the results reported here indicate that it is worthy of more extensive trial.

Summary

In a group of disturbed psychiatric patients the effects were compared of reserpine and " serpina ", a preparation of the total alkaloids of *Rauwolfia serpentina Benth.* The response to each drug was similar, but " serpina " was free from side-effects.

The response to " serpina " and absence of side-effects were confirmed in a larger group treated for 22 weeks.

Further trial and investigation of this drug are warranted.

I am indebted to Dr. D. Macmillan, the Physician-Superintendent, for his interest and help in these trials, to Dr. D. Moynagh for his cooperation, and to Dr. J. Komieniecki for carrying out psychometric tests on some of these patients, I wish to thank the nurses who made many of the observations.

The " serpina " was kindly supplied by Messrs. Hillside Pharmaceuticals, and the " reserpine " and the placebo tablets by Messrs. Riker.

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THE SYNDROME OF ACUTE CENTRAL CERVICAL SPINAL CORD INJURY

BY

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Any discussion of the diagnosis and treatment of spinal cord injuries inevitably involves controversial matters. Among the foremost of these are the indications for (Schneider, 1951, 1955) and the contraindications for (Schneider, Cherry, and Pantek, 1954) surgical intervention. It seems highly important, therefore, to establish criteria which will assist in determining whether an operation should or should not be undertaken. In 1955, a paper was published on "The Syndrome of Acute Central Cervical Spinal Cord Injury" (Schneider *et al.*, 1954), a syndrome the presence of which contraindicated any surgical procedure. At that time, nine of the authors' cases which exhibited this neurological pattern were described in detail, and six others were abstracted from the literature. There was no pathological material presented, however, which would substantiate firmly the clinical thesis which had been advanced.

This paper is written to present 12 additional patients who exhibited the syndrome. In one case the post-mortem examination confirms the assumptions previously made on the basis of clinical examination. A study of this group of cases permits further consideration of the mechanisms involved in this type of injury.

The description of the syndrome reads:

> "In acute cervical spinal cord injuries, there is a syndrome that suggests acute central cervical spinal cord involvement. It is characterized by disproportionately more motor impairment of the upper than of the lower extremities, by bladder dysfunction, usually by urinary retention, and by varying degrees of sensory loss below the level of the lesion. If the findings are caused by central cord destruction with bleeding, hematomyelia, there may be caudad or cephalad extension of the lesion with further progression of symptoms, perhaps culminating in complete tetraplegia or death. But if the symptoms are caused by concussion or contusion, with an edematous type of central cord involvement, there may be gradual return of function in a definite sequence. The amount of recovery depends on the degree of edema present compared to the extent of true destruction of nervous tissue. The lower extremities tend to recover motor power first, bladder function returns next, and finally strength in the upper extremities reappears, with the finer finger movements coming back last. The varying degrees of sensory impairment do not follow any set pattern of recovery."

It was first thought that the acute central cervical spinal cord injury was found only in severe hyperextension injuries. The importance of suspecting such an injury of the cervical spine in the presence of facial lacerations or contusions of the forehead has been emphasized by Taylor and Blackwood (1948). When the hypertrophic arthritic cervical spine is hyperextended, there may be simultaneously compression of the anterior cord caused by a posteriorly placed bony spur and a posterior impingement upon the cord caused by a wrinkling of the ligamentum flavum. This mechanism was effectively demonstrated in myelography on cadavers by Taylor (1951). In younger specimens there was no distortion of the pantopaque column in the cervical spinal canal when the head was placed in a flexed or neutral position. When the cervical spine was forcibly hyperextended, however, there was definite encroachment posteriorly upon the pantopaque column in the spinal canal. Taylor suggested that this was probably caused by a bulging forward of the ligamentum flavum. When a cervical myelogram was made similarly in hyperextension in an elderly patient with posterior hypertrophic spurring of the cervical vertebral bodies, the bony spur anteriorly and the wrinkled ligamentum flavum posteriorly encroached simultaneously in the canal.

There are other mechanisms which may result in a squeezing of the cervical spinal cord. The acute central cervical spinal cord injury syndrome may occur in severe cervical compression fractures and in some cervical fracture-dislocations. It is difficult to postulate in cervical compression fractures whether the cervical spinal cord is squeezed in hyperextension or in flexion of the cervical spine.

Cases of cervical fracture-dislocation, however, are a different matter. The acute central cervical cord injury syndrome may occur in an acute flexion injury accompanied by fracture-dislocation. The cervical spinal cord is acutely squeezed anteriorly by the lower involved, or caudad, vertebral body of a cervical fracture-dislocation and posteriorly by the lamina of the upper, or cephalad, involved vertebra.

The 12 patients presented here were admitted to four different hospitals in the year following the publication of the article on the acute central cervical cord injury syndrome (Schneider *et al.*, 1954).

Case Reports

Case 1.—On May 3, 1955, S. B., a 63-year-old woman, fell headlong downstairs, striking upon her face. The patient developed complete tetraplegia accompanied by numbness of the lower extremities. Within two hours after the fall she was examined at Wayne County General Hospital, and the following positive findings were noted: a large contusion on the left forehead, slight paresis of the lower extremities, marked weakness of the upper extremities, and complete paralysis of the hands. There was a complete areflexia with no pathological reflexes. Hypaesthesia was noted from the shoulder downward. Position sense was intact. A radiograph of the cervical spine showed hypertrophic spurring at the C_3-C_4, C_4-C_5, and C_5-C_6 interspaces.

Several hours after she was admitted, her legs began to move readily, and on the following day they were strong. The upper extremities, however, showed almost complete paralysis of the forearm and hand muscle groups. Twenty-four hours after admission the hypaesthesia which had been present below C_7 bilaterally began to diminish gradually in the lower extremities. It was necessary to insert an indwelling catheter in the bladder.

A lumbar puncture on May 5, 1955, produced cerebrospinal fluid with 21 R.B.C.s per high-power field and a total protein value of 83 mg. per 100 ml. The blood Kahn test was 3 plus, but the spinal fluid Kahn test was negative. A jugular vein compression test showed no block. Twelve days after the injury movements in the patient's hands began to improve. By May 18, bladder control was good. A myelogram performed three weeks after injury with the patient in a steep Trendelenburg position showed that the pantopaque did not pass the level of C_6 until the neck was flexed. A defect was present at the C_3-C_4 interspace on the lateral view with a " step ladder " pattern on the anterior-posterior view.

By July 7, 1955, the patient moved her hands only weakly, but all other muscles of the extremities were normal. Pyramidal tract signs were observed in the left lower and upper extremities.

Case 2.—J. D., 55 years old, fell headlong down 23 steps on January 22, 1955. He remembered striking upon his forehead and left temple so that his neck was thrown into marked hyperextension. He was completely numb and paralyzed from the neck downward at the time when he was admitted to a local osteopathic hospital. Twenty-four hours after he was injured he could move the thumbs and toes. It was necessary to insert an indwelling catheter into the bladder. The strength in the lower extremities increased much more rapidly than in the upper, so that within a period of two weeks he could manipulate his lower extremities quite well. He could raise his arms to a certain extent. All forearm movements were poor, however; and, although his thumbs could be wiggled slightly, he could not move his fingers.

The patient was treated with intermittent halter traction until the time of his transfer to the U.S. Veterans Hospital, Ann Arbor, Michigan, on February 10, 1955. When he was admitted, a disproportionately better movement was noted in the lower extremities than in the upper, and his hands were very weak. Hypalgesia and hypaesthesia were observed over the upper extremities and, in a lesser degree, over the trunk and lower extremities. The deep reflexes were symmetrically hyperactive and no pathological reflexes were apparent. Vinke tongs were inserted. Radiographs of the cervical spine demonstrated a hypertrophic arthritis with spurring at all the interspaces but no evidence of fracture-dislocation.

A follow-up examination was made on March 4, 1956. His gait was impaired because of weakness in dorsiflexion of the right great toe and foot. Strength was less in the upper extremities than in the lower ones. The small hand muscles on the right side were atrophied. Vibration and position sensations were intact. The remainder of sensation had returned in patches. There was a zone of hyperaesthesia from T_{10} through T_{12} dermatome bilaterally. Hypalgesia was demonstrated over the dorsum of the right foot, leg, and knee, and bilaterally below the T_{12} dermatome. The deep tendon reflexes were more hyperactive in the right upper and lower extremities than in those on the left. There were definite pathological reflexes in both upper extremities and in the right lower, with equivocal abnormality in the left lower extremity.

Case 3.—L.R., 61-year-old farmer, was working on his manure spreader on Friday, April 13, 1956, when he fell headlong to the ground forcing his neck into extreme hyperextension. He could not move his arms or legs. After a short time he found he could move his legs weakly and attempted to roll over, but he was unable to do so. Four hours later the patient was taken to the hospital. He felt sharp shooting pains in his arms and legs. Upon sensory examination, however, there was a complete loss of sensation in both upper extremities. He could flex and extend his lower extremities and could move his shoulders but he could not move his forearms, wrists, or fingers. He had no pathological reflexes. Position sense was absent in both upper and lower extremities. Vibration sense was present in the left upper extremity, but absent over the remainder of the body. Complete thermanaesthesia was demonstrated below the level of T_1 dermatome bilaterally. He had hypalgesia over the left C_6 and C_7 dermatone and hypalgesia to L_3 on the left and T_{12} on the right side.

Radiographs of the cervical spine showed extensive degenerative and hypertrophic changes. No evidence of any fracture-dislocation was observed. Dr. Adam

McClay, the orthopaedic consultant, made a diagnosis of acute central cervical cord injury and stated that the prognosis was good. He advocated conservative treatment.

An examination on April 15 showed that the sensory pattern was essentially unchanged. The patient had powerful quadriceps and flexor movement in the lower extremities but still no detectable movement in the upper ones.

Case 4.—On March 23, 1956, H. S., a 51-year-old man, fell head first down a long flight of stairs while under the influence of alcohol. He regained his senses six hours later in a Detroit hospital, suffering from numbness and tingling from the neck downward over his body, marked weakness of his arms, paralysis of his hands, and slight paresis in his right leg. He had right-sided hyperactive deep tendon reflexes and a right extensor plantar reflex. A lumbar puncture was made within the first 24 hours after his injury, and the cerebrospinal fluid contained 60 red blood cells and 3 white blood cells per high-power field. The protein content of the fluid was 117 mg. per 100 ml. He had no bladder control during the first 48 hours in hospital. The motor power in his legs improved markedly within the first 24 hours, but he still had marked paresis in the right arm and moderate weakness of the left hand. A diagnosis was made of " conversion hysteria, possibly superimposed on some cord damage".

On the sixth day after injury, the patient was transferred to Wayne County General Hospital. Radiographs of the cervical spine demonstrated posterior hypertrophic spurs on C_4, C_5, and C_6 vertebral bodies, with no apparent evidence of fracture-dislocation.

On April 6, 1956, two weeks after he sustained the injury, the patient had only 5% normal strength in the muscle groups of the right arm. He had only minimal motion of the right thumb and fingers. The muscle groups of the left arm showed about 75% normal strength, in contrast to the lower extremities, where there was minimal paresis bilaterally. With the exception of the hypalgesia below the left knee, a sensory examination demonstrated normal responses. He had no biceps reflexes, but triceps reflexes were present, the left being more active than the right. The lower extremities had hyperactive deep tendon reflexes, the right quadriceps reflex being more active than the left. There were bilateral extensor plantar reflexes. After four days, he showed marked improvement in the strength of the right arm, although the hand grip was still weak.

Case 5.—E. B., a 52-year-old lumberman, fell 12 feet from a loaded pulp truck on the morning of March 2, 1956. He was unconscious for about an hour and did not recall in what position he had struck the ground. Upon regaining consciousness he found that he was temporarily unable to move all four extremities; his toe movements returned almost immediately, however. Within four hours he recovered motor power, first in the left leg, then in the right, so that he was able to stand erect four hours after injury. He could move his arms but they were much weaker than his legs. Finally, he was able, with assistance, to walk 250 feet to a car in which he was taken to a local hospital. Radiographs of the spine were taken and he was put to bed. No lumbar puncture was made.

During the first seven weeks in hospital the patient felt numb from the neck downward over his body, and was unable to use his arms, although he moved his legs slightly. Three and a half months after his injury he noted a generalized tingling sensation below the level of T_{10} dermatome anteriorly and T_8 dermatome posteriorly. He began to walk unassisted about four months after the accident. His chief complaint was that he felt hot, prickly, and swollen sensations in the right leg. An indwelling catheter had to be used during the first two months of his stay in hospital until the bladder regained its function.

The patient was transferred to the University of Michigan Hospital, where the following neurological findings were noted: weakness in the legs and trunk, more marked paresis in the upper extremities, and maximal impairment of strength in the hands. There was hypaesthesia along the ulnar aspect of the right hand and a hypalgesic level at T_3 segment bilaterally. Dysaesthesia was found over the right leg. He had no vibratory sensation over the ankles, but position sense was present in both feet. With the exception of the Achilles reflexes, all deep reflexes were symmetrically hyperactive. Bilateral pyramidal tract signs were demonstrated in both upper extremities and he had an equivocal extensor plantar reflex in the right lower extremity. Radiographs of the cervical spine showed hypertrophic vertebral body spurring at C_3-C_4 and C_5-C_6 interspaces.

Case 6.—At 11.30 p.m. on October 11, 1955, J. H., a 72-year-old man, fell from a wagon, striking on his head. He was not unconscious but he was immediately paralyzed in all four extremities with numbness from the neck downward. While in transit to the University Hospital in the ambulance, he began to move his toes and legs. When he was admitted to the hospital, the patient was alert and cooperative. He had no movement in the upper extremities or in the intercostal musles, but there was some motion in the hamstrings, quadriceps, adductors of the hips, and dorsiflexor muscles of the feet. On the left side from the T_2 to L_3 dermatome, he had a zone of loss of sensation to pinprick and dysaesthesia of temperature, and a loss of all sensory modalities of the remainder of the trunk and extremities. The deep reflexes in the extremities were equal, although symmetrically hyperactive in the legs. He had no pathological reflexes. A diagnosis was made of acute central cervical cord injury at C_3-C_4 or C_4-C_5 interspaces. Halter traction was applied.

Radiographs of the cervical spine demonstrated a fracture of the C_2 and C_3 spinous processes, and showed also some mild evidence of hypertrophic spurring of the vertebral bodies at C_4-C_5 and C_5-C_6 interspaces, with slightly more lipping at the C_6-C_7 interspace (Fig. 1). A lumbar puncture was performed and when jugular compression was applied, the cerebrospinal fluid rose and fell normally. Vinke tongs were substituted for the halter traction and, within 10 hours after admission, intercostal function had returned. A cystometric

FIG. 1.—Case 6: Lateral radiographs of the cervical spine demonstrating fractures of C_3 and C_5 spinous processes and mild spurring at the C_4-C_5 and C_5-C_6 interspaces with more marked lipping at the C_6-C_7 interspace.

examination demonstrated a 180 ml. capacity reflex type of bladder on October 15, and the examining urologist concluded that the patient might be experiencing some return of function. Five days later there were uninhibited contractions suggesting a neurogenic reflex type of bladder. On October 25 bladder sensation partially returned. The bulbo-cavernous reflex was intact. The strength in the patient's legs improved but his arms remained paralyzed. On October 30, his temperature rose to 103° F. and his blood pressure fell. The chest radiograph showed right atelectasis and pneumonia. The electrocardiograph was normal. The patient became progressively worse and died on November 9. He had sustained a pulmonary embolus complicated by atelectasis and pneumonia.

Necropsy Examination.—This disclosed more marked bony ridges at the C_4-C_5 and C_6-C_7 interspaces than were demonstrable radiologically. The surface of the spinal cord appeared to be normal, but the cord was soft (Fig. 2). Cross sections of the cervical spinal cord taken at the upper C_4 segment revealed, macroscopically, a fairly normal cord, somewhat flattened transversely and soft to palpation (Fig. 3). Cross section of the spinal cord just below this level exhibited necrosis of the central portion which extended toward the posterior surface to include parts of the posterior and postero-lateral funiculi. Sections above and below this segment exhibited only pallor of the funiculi.

Sections of the spinal cord were cut and prepared histologically with haematoxylin and eosin, Masson trichrome, and Weil stains. The sections of the lower fourth cervical segment of the spinal cord showed a large destructive lesion, which, at its maximum, included the central portion of the grey commissure, the anterior horns, the posterior horns, and the posterior columns of the cord (Fig. 4). A few millimetres below this level, the lesion appeared well circumscribed in the central portion of the cord immediately behind the central canal (Fig. 5). The lesion included the more proximal portions of both posterior horns and the medial parts of the posterior columns and the postero-lateral columns.

Microscopic examination of these areas showed almost complete destruction of the substance of the cord with liquefaction and necrosis. This area was filled with

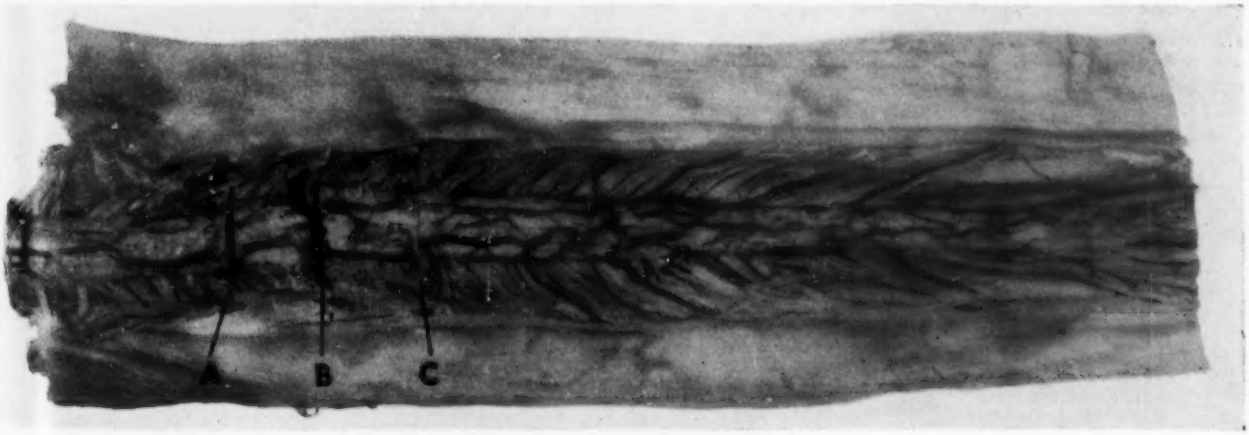

FIG. 2.—Case 6: The necropsy specimen showing that there was actually little evidence of gross external damage apparent to the dorsal surface of the cervical spinal cord. The three incisions *A*, *B*, and *C* through the involved area unfortunately were made before photographing the specimens.

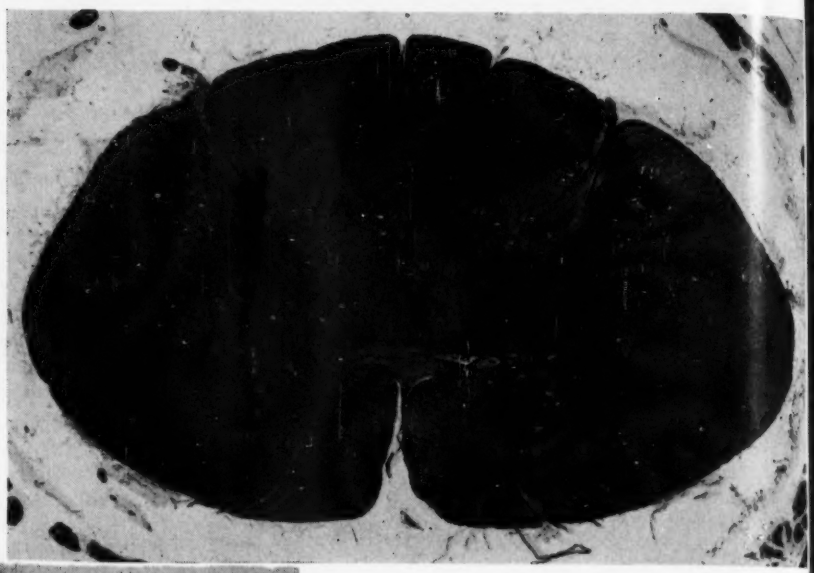

FIG. 3.—Case 6: This shows the microscopic section of the cervical spinal cord at the upper C_4 level (*A*). The general pattern shows little evidence of destruction to the cord itself.

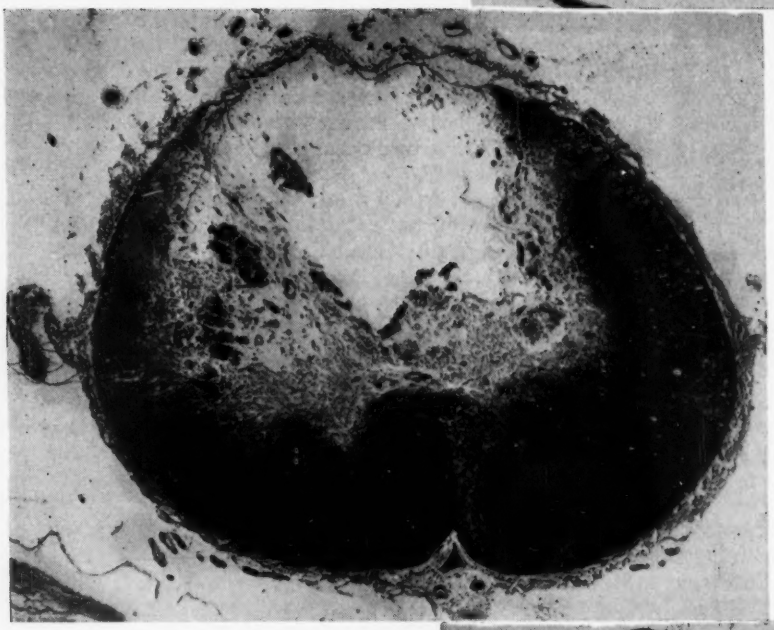

FIG. 4.—Case 6: A section taken at the lower C_4 segment (*B*) demonstrating an intact pia mater but complete destruction of the cord centrally and dorsally in the posterior columns. The destruction spread into the lateral columns leaving isolated islands of intact fibres. The preservation of the more peripheral or lower extremity portions of the lateral cortico-spinal tract indicates the basis for the symptoms and neurological findings in this syndrome. There is no thrombosis of the anterior spinal artery.

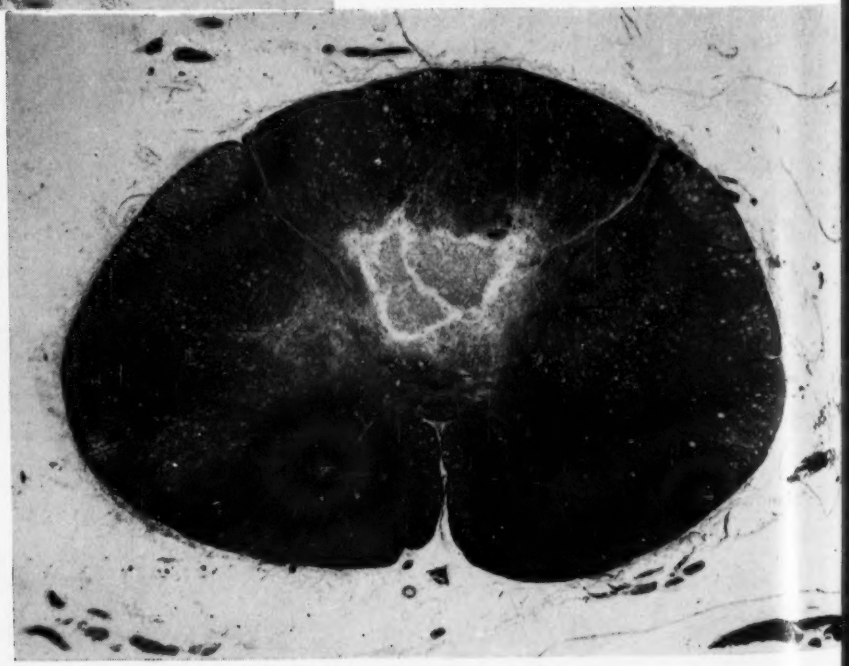

FIG. 5.—Case 6: The microscopic section of the upper portion of the C_5 cord segment (*C*) shows central necrosis and destruction extending above the central canal and laterally toward the lateral cortico-spinal tract on the right side. There is a patent anterior spinal artery.

debris and numerous macrophages (gitter cells). The limits of the lesion were not well delineated from surrounding areas. Numerous small arterioles and newly-formed blood vessels were seen in this area. Many of these had hyalinized walls and appeared markedly congested. The blood vessels were more abundant in the transition zone between the necrotic centre and the surrounding cord tissue. The anterior horn cells were diminished in number and those remaining showed marked retrogressive changes. In the area of maximum involvement the anterior horns had completely disappeared and had been replaced by a mass of gitter cells, debris, and newly-formed blood vessels. At the marginal zone of the cord there was some degeneration of the myelin sheaths in the posterior and postero-lateral columns. The myelin degeneration of the postero-lateral columns was more prominent in the deeper portions of the columns and merged into the gross lesion.

The leptomeninges were thickened with fibroblastic changes. The meningeal vessels, including the anterior spinal artery, posterior spinal arteries and veins, appeared to be normal but congested. The dura was normal in appearance.

Sections of the cord one segment below and one segment above the lesion showed marked congestion and moderate oedema. There was some loss of myelin in both postero-lateral columns, mostly in the deep portions. The anterior and posterior horns appeared well preserved in relation to the number of cells. The neurones showed changes compatible with ageing. The leptomeninges likewise exhibited changes of marked congestion and moderate oedema.

Case 7.—R. D., a 36-year-old severely paranoid schizophrenic male patient at the Veterans Hospital in Battle Creek, Michigan, was assaulted by another patient on January 21, 1954, and, during the ensuing scuffle, struck his head on the floor. The physician who examined him shortly afterwards stated that the patient was livid, had an irregular, thready pulse, and was incontinent of faeces. As the patient gradually regained consciousness, he complained of headache and pain radiating down the neck. There was no abnormality noted when the neurological examination was made. About 2 a.m. on January 22, 1954, the patient stated that he could not move, but he actually was seen moving his extremities. At 4 a.m., the patient could void only very small amounts, and later he was incontinent of a large amount of urine. On January 23, two days after the injury, he was unable to move either arm voluntarily. He also had a loss of pain and temperature sensation in the left arm, hyperactive patellar and ankle jerks, and a temperature of 104·8° F. By the next day he had marked weakness and flaccidity of the upper extremities but could move his legs. A lumbar puncture disclosed a clear cerebrospinal fluid with no block shown by the jugular compression test. Cervical spine films made on January 26 demonstrated a "crown" compression fraction of the C_5 vertebral body.

The patient was transferred to the Veterans Hospital in Ann Arbor, Michigan, and on admission was seen to have flaccid paralysis of both upper extremities with normal tendon reflexes, weakness in both legs, with spasticity and increased tendon reflexes and bilateral ankle clonus. On February 6, 1954, a neurosurgical consultant made a diagnosis of hyperextension injury of the cervical spine with compression fraction of C_5 vetrebral body and central cord destruction or haematomyelia. By February 24, 1954, he walked with assistance. In March the patient had regained bladder control; and by May, 1954, he could feed himself.

Two years after the accident he exhibited more weakness in the upper than in the lower extremities, a spastic gait, a slight decrease in vibration sense in the right upper and lower extremities, symmetrically hyperactive reflexes, and a left extensor plantar reflex.

Case 8.—At 8.30 p.m. on July 9, 1954, E. S., a 12-year-old boy, dived into two feet of water and sustained an immediate paralysis of the upper extremities, but retained minimal movement in the legs. On admission to St. Joseph's Mercy Hospital, Ann Arbor, Michigan, he had only movements at the shoulders with no extension of the upper extremities or motion of the fingers. He had slight internal rotation in the thighs and the toes of both feet moved slightly. A level of hypaesthesia and hypalgesia was demonstrated extending to the T_7 dermatome bilaterally but motion and position sense were preserved. He had equally hyperactive deep reflexes. No extensor plantar reflex could be demonstrated. Priapism was present.

Radiographs of the cervical spine revealed a fracture-dislocation of C_2 vertebral body anteriorly on C_3 and compression fractures of C_4, C_5, and C_6 vertebral bodies with protrusion of the C_5 centrum posteriorly into the spinal canal. The posterior rim of the axis was in close proximity to the occipital bone.

A diagnosis of acute central cervical cord injury was made. A guarded prognosis was given to the patient's parents but the chance of recovery was considered good with the classical pattern of motor return predicted. The surgeon inserted Vinke tongs on the night of admission. By July 11, the priapism had subsided and there were bilateral extensor plantar reflexes. On July 12 a lumbar puncture revealed a bloody fluid (traumatic tap) without evidence of block when the jugular vein compression test was made. Five days later the patient had slightly better dorsiflexion in the left foot than in the right. On July 26, the day before transfer to another city, a cystometric examination revealed a reflex neurogenic bladder.

Reports from the Mary Free Bed Hospital in Grand Rapids, Michigan, where the patient was observed during his convalescence, indicated that he was able to move his fingers on August 17. By January 25, 1955, he could walk unassisted. At the time of his discharge on July 7, 1955, he had some slight residual weakness in his hands, but he performed all necessary functions readily.

Case 9.—C. L., a 52-year-old taxi driver, was examined at St. Joseph's Mercy Hospital, Ann Arbor, Michigan, on August 21, 1955, having been transported 500 miles without the benefit of any type of cervical immobilization. He had sustained an injury in an automobile accident five days before he was brought to the hospital.

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He had been rendered unconscious immediately, had a lucid interval, and then became semiconscious for 24 hours. His lower arms and hands were totally paralyzed, but he could move his lower extremities slightly. During the five days before his transfer, he improved markedly. Upon arrival in Ann Arbor, there was minimal strength in the grip and in the arms, but he had good motor power in both legs. There was hypalgesia over the C_6, C_7, and C_8 dermatomes bilaterally and the entire right side of the trunk. The deep reflexes were symmetrically hypoactive with no pyramidal tract signs in the upper or lower extremities. Cystometric examination was normal. A diagnosis of acute central cervical spinal cord injury was made, and the prognosis was stated to be good.

Radiographs of the cervical spine showed a marked anterior fracture-dislocation of the C_5 vertebral body anteriorly on the compressed vertebral body of C_6. There were also fractures and posterior displacement of the laminae of C_5 and C_6 bilaterally, and a fracture of the C_4 spinous process. Skeletal traction was applied. Decompressive laminectomy was deferred until August 31, 1955, to permit improvement in the patient's general condition. At operation the laminae of C_4, C_5, and C_6 vertebrae were found to be fractured and displaced posteriorly. The dura was opened, the arachnoid was sectioned laterally, and after the dentate ligaments were cut, the cord pulsated readily. The dura was closed tightly and spinal fusion was performed. He was discharged from the hospital on December 11, 1955. Radiographs of the cervical spine after fusion showed that the graft was calcifying nicely. Three months later the patient was able to return to his job as a taxi driver and was bothered only by some stiffness of the neck.

Case 10.—J. D., a 17-year-old student, was admitted to the University of Michigan Hospital on August 4, 1955, one hour after diving into shallow water. He was paralyzed immediately in all four extremities and had to be carried from the water. On admission to the hospital the patient had diaphragmatic respirations. There was a complete areflexic tetraplegia with a sensory level at the C_7 dermatome bilaterally and the patient was unable to void. Head halter traction was applied immediately, and radiographs demonstrated a subluxation of the C_5 vertebral body anteriorly on the slightly compressed C_6 vertebra. Thirty minutes after the application of the cervical traction he experienced a complete return of sensation. The halter traction was replaced by a Vinke skeletal tractor. A lumbar puncture revealed a complete block on the jugular vein compression test.

Twelve hours after he was admitted to the hospital, the patient had a decompressive laminectomy of C_5 and C_6 vertebrae. The right C_5-C_6 facet was locked. The dura was opened in the midline, the dentate ligaments cut, and the subluxation reduced by traction and careful prying with an osteotome. The pulsating cord appeared slightly hypaeremic and swollen. The dura was not closed.

Within 24 hours after the operation had been performed, the patient began to move his left foot and superficial as well as deep sensation returned on his right side. Four days after the injury he still had hypalgesia to the C_7 dermatome. Deep pain and position sensations were intact in the lower extremities. He showed marked recovery of motor power in the legs, but less in the upper and forearm muscles, and no return of function in the fingers or triceps muscles. The deep reflexes were equal and active and he had bilateral extensor plantar reflexes. The first finger movement appeared on August 16, and cystometric examination showed a normal bladder. The patient left the hospital on October 18 with his neck supported by a Forester collar. On December 9, 1955, he walked readily without a cane, and his hand function, which was the greatest residual deficit, was 65% of normal.

Case 11.—I. W., a 40-year-old man, dived into the Detroit River on August 8, 1955, and had to be pulled from the water because of total paralysis in all four extremities. He was admitted to the City of Detroit Receiving Hospital at 7 p.m. He had a complete tetraplegia with deep reflexes that were equal and active in the upper extremities, but the right lower extremity was areflexic. On catheterizing the bladder at 12 p.m., 800 ml. of urine was removed. Radiographs of the cervical spine revealed the C_4 vertebral body dislocated anteriorly on C_5. Skeletal tong traction was applied and a 35-lb. weight added. Serial radiographs of the cervical spine were taken of the facets. There was complete reduction of the cervical fracture-dislocation and good realignment of the cervical spine so that the weight was reduced to 10 lb. The patient had no proprioception, a level of hypalgesia to the C_3 dermatome bilaterally, and complete areflexia.

On August 10, a lumbar puncture showed no evidence of blockage of the subarachnoid space on the jugular compression test. The spinal fluid was clear with only 4 red blood cells per high-power field and a total protein level of 102 mg. per 100 ml. At midnight of the same day the patient had respiratory distress and difficulty in swallowing. It was decided that surgical intervention was not indicated.

On August 28, the patient had a slight return of motor power and sensation in the lower extremities. By September 4, these functions were markedly improved. The skeletal tongs became disengaged on September 10, and it was thought advisable to discontinue their use. By September 19, 1955, the patient had regained some degree of motor power in both the upper and lower extremities, exclusive of hand movement. The indwelling catheter was removed.

At the time he was transferred to Wayne County General Hospital on September 22, 1955, he definitely had greater strength in the legs than in the upper arms, but the fingers and hands were still paralyzed. Pain and touch sensations were normal, but he had no position sense in the fingers of his right hand. The deep tendon reflexes were equal and active in the arms, but hyperactive in the legs. He showed bilateral Hoffmann responses and extensor plantar reflexes. The patient rejected the cervical spinal fusion operation which was recommended, and was discharged in a Taylor back brace with a Forester collar, on October 21, 1955.

On March 6, 1956, examination showed that the

patient had weakness in all four extremities, but there had been progressive improvement in strength, and that now he could move his hands and fingers. Sensation was normal in all modalities. He had persistent pyramidal tract signs in all four limbs, with sustained left ankle clonus. Cervical spinal fusion was again advocated and this operation was performed on March 13, 1956.

Case 12.—Mr. X, a 68-year-old man, stumbled and struck his head and neck on the sidewalk on November 25, 1955. He was admitted to his community hospital where he complained of pain in the neck which radiated into both arms and hands. He also had paresis of the left arm and leg. Radiographs of the cervical spine demonstrated a fracture-dislocation of C_5 vertebral body anteriorly on C_6. Skeletal tong traction was applied and a 20-lb. weight added.

On the day after he was injured the patient required catheterization. Three days after injury he began developing mental disorientation, which was believed to be caused by cerebral anoxia secondary to decreased respiratory function. On December 2, 1955, he complained of severe pains in his arms and legs. A nurse's note stated on December 6 that the patient had fairly good control of his legs and often moved them but that he had less power in his arms. The right fingers and toes " were stiff ". He continued to cry out because of severe pain in the extremities, and both physicians and nurses interpreted this as a result of mental confusion. On December 8, 1955, the patient had severe chest pain with associated dyspnoea. By that time all motor power had been lost in the lower extremities, but pain was still present. An electrocardiogram two days later showed a right bundle branch block. He continued to have severe discomfort throughout the entire trunk and extremities.

On New Year's Day, 1956, the skeletal tong traction was removed, and six days later, the patient had pain in the feet, legs, and arms and " he talked only of pain ". Flexor spasms occurred in both knees but he had some voluntary movement in both, and marked improvement in feeling in both lower extremities. By January 10, 1956, the patient could move both lower extremities, had good motor power in the shoulders, poor elbow extension, fair motion in the forearm, but had no finger movement whatever on the left side.

The patient was transferred to Wayne County General Hospital in January, 1956. The indwelling catheter was removed. There were muscle contractures in both elbows, hips, knees, and to a lesser extent, in both hands, making evaluation difficult. Radiographs of the cervical spine, four months after trauma, demonstrated complete reduction of the dislocation with calcification to the vertebral body both anteriorly and posteriorly.

An examination on April 6, 1956, demonstrated that the patient's strongest movements were in the lower extremities in plantar and dorsiflexion of the feet. The other muscle groups of the lower extremities were weak. He had slight weakness in both forearms with marked paresis in the hand grip bilaterally. Hypalgesia was noted below the T_8 dermatome on the right. Touch was intact. Position sense was absent in the toes. Vibration sense was present in the knees. He had normal biceps reflexes, no triceps reflexes, and symmetrically hyperactive patellar and Achilles reflexes. Positive extensor plantar reflexes were demonstrated.

Discussion

Mechanisms.—In recent years an increasing amount of interest has been focused on the problems of chronic anterior cervical cord compression by hypertrophic spurs (Bedford, Bosanquet, and Russell, 1952; Brain, Northfield, and Wilkinson, 1952; Kahn, 1947; Spillane and Lloyd, 1952; Symonds, 1953), but too little attention has been devoted to acute traumatic lesions of the cervical spinal cord in such cases.

Case reports 1 to 6 concern patients who had had hypertrophic cervical arthritis and developed acute central cervical cord injury on the basis of hyperextension injury to the cervical spine. In Cases 1, 2, 3, and 6, the patients had suffered definite facial or forehead injuries, supporting the belief that hyperextension injury had occurred. The patient in Case 4 had been drinking; and in Case 5 the man had been rendered unconscious, and therefore an accurate history concerning this specific point could not be obtained.

All these case reports demonstrate how acute central cervical spinal cord injury may occur in hyperextension of the hypertrophic arthritic spine without compression fracture or fracture-dislocation, giving support to Taylor's (1951) thesis. They should also serve as a warning against a too vigorous hyperextension of the cervical spine in the intubation of elderly patients for the administration of intratracheal anaesthesia. Reports have appeared in the literature calling attention to contingent dangers, and one of the authors (R. C. S.) is presenting elsewhere a case in which such an anaesthetic technique resulted in acute central cervical cord injury, though the patient gradually recovered.

The patient in Case 7 sustained a " crown "-shaped cervical compression fracture, and it could not be determined whether or not this injury occurred with hyperextension or flexion of the cervical spine.

The syndrome probably resulted from acute flexion injury to the cervical spine and spinal cord in Cases 8 to 12. The patient reported in Case 8 had multiple mild compression fractures and fracture-dislocations resulting in a " step " type of injury with multiple points of simultaneous anterior and posterior compression of the cervical spinal cord. In Case 9, an acute flexion injury must have occurred, accompanied by a severe fracture-dislocation of the cervical spine, along with a momentary holding of the laminae of the more cephalad vertebra. This

squeezed the cord. An associated avulsion of the laminae must also have been present, causing compression of the cord, with the result that it was spared from complete transection. The fracture-dislocations in Cases 10 and 11 are the disruptions which are commonly found and result in a simple squeeze of the cord rather than in transection.

In Case 12 the patient suffered initially a fracture-dislocation of a hypertrophic cervical spine with little immediate neurological deficit. After the fracture-dislocation was reduced, however, the cord was probably drawn into some hyperextension over the hypertrophic spur so that an acute central cervical cord injury syndrome gradually developed. After skeletal traction was removed, the patient began to regain function following the characteristic recovery pattern.

Age.—A glance at the ages of these patients is instructive. In Cases 1 to 6, the ages were 63, 55, 61, 51, 52, and 72 years, respectively. As might be expected, these were the individuals with hypertrophic cervical spines who sustained acute central cervical cord injuries in hyperextension, without fracture or fracture-dislocation. The ages in Cases 7 to 11 were 36, 12, 52, 17, and 40 years, respectively, a much younger group as a whole. These individuals exhibited the syndrome in association with compression fracture or fracture-dislocation, more than possibly resulting from an acute flexion mechanism. The patient reported in Case 12 was 68 years old but his case was exceptional in that there was a fracture-dislocation of a hypertrophic cervical spine.

Anatomy.—In the cervical spinal cord there is a definite segmentation or pattern of fibres within the lateral corticospinal tract. The lumbar fibres, or those which supply the lower extremities, lie laterally in the cervical spinal cord. The thoracic or trunk fibres are in a medial position, while the cervical or upper extremity fibres assume a still more medial location with the finger fibres placed centrally. When the cervical spinal cord is squeezed from an anterior and a posterior position simultaneously, there may be a central zone of cord destruction surrounded by a more peripheral one of spinal cord oedema. The degree of permanent disability which these patients incur will depend upon the extent of central cervical cord damage, so that as the more peripheral zone of oedema recedes, the more peripherally located fibres in the lateral corticospinal tracts and adjacent tracts will regain function. As a result, the legs will regain function first, then bladder function returns, the arms recover next, and finger movements are regained last.

In order to study the various stresses which occur when the spinal cord is subjected to anterior-posterior compression, a sponge rubber model was constructed by Pantek (Schneider *et al.*, 1954). Upon this model had been painted a diagram of the cervical spinal cord and its various fibre tracts. About its periphery was a fine rim of firmer rubber which served to represent the pia mater and the points of attachment of the dentate ligaments. The model was then placed into a wooden vice so that an anterior and posterior compressing force could be applied. By placing a grid over the model, it was possible to measure types and degrees of distortion. The study revealed the presence of at least four definite stresses, the predominant one being—as one might expect—the anterior-posterior compressive stress (Schneider *et al.*, 1954).*

The use of this model obviously has its limitations, for no observations can be made concerning the influence of stress on the vascular components of the cord, the comparative looseness of texture near the vicinity of the central canal versus the compactness of fibre bundles near the periphery, or the fact that many of the sensory fibre tracts lie near the periphery of the cord so that they are affected merely by oedema rather than undergoing complete destruction. Ideally, the use of strain gauges in experimental animals would be an excellent method of evaluating these stresses but at the present time even the smallest of these is too bulky to be used in experiments with animals. The employment of the sponge rubber model and an analysis of the clinical study which has been published elsewhere have given us only a small part of the information which we require.

Pathology.—For many years physicians have sought an explanation as to how the cervical cord can be damaged with apparently no attendant injury to the cervical spine. Holmes (1915) discussed this problem, stating that if the spinal cord were concussed, there might be either no gross evidence of cord damage or a uniform swelling opposite the point of impact of the cord against the bone. He suggested that since the spinal cord lay in a water-jacket of cerebrospinal fluid, it might oscillate to and fro in the fluid when the trauma occurred. These movements might become asynchronous with the motion of the cervical bony spine, and the spinal cord would then impinge upon the bone, causing concussion or contusion, and thus produce physical disturbance " especially in the fluid axioplasm of its fibres ". Holmes observed that the greatest pathological change was a pronounced oedema in the affected segments, the most marked involvement

*The reader is referred to the original article for a complete discussion of this problem.

being found directly at the site of the blow. In his microscopic preparations of damaged cords, some of the fibre tracts had been destroyed but in the remainder of the fibres the myelin sheaths and axis cylinders were swollen. In the grey matter there were focal areas of softening, usually associated with haemorrhages which had peripheral zones of neuronal degeneration. These pathological findings could account for the presence of neurological signs which partially or completely disappear as severe oedema subsides. This is what occurs in the syndrome of acute central cervical cord injury.

Nerve fibres which have been compressed or squeezed are more likely to recover function than are those which have been acutely and severely flexed so that the neurons are " fractured " and permanent damage is sustained. A vascular impairment of the spinal cord is probable in patients thus affected. In Case 6 not only the central elements of the spinal cord but also the posterior columns were destroyed. Woodward and Freeman (1956) have shown that when the peripheral nerve roots and their associated neuronal sheaths were ligated over a zone of six segments (in dogs), central cavitation might appear along with some loss of the posterior columns. They attributed this loss to venous congestion in these regions. The posterior surface of the cord is drained by paired posterior veins which are not nearly as large and efficient in function as the large anterior venous channels. Woodard and Freeman's work has not proved conclusively that the changes were caused only by venous congestion, for certainly some degree of the arterial supply as well as the venous drainage must have been impaired when six peripheral nerve roots and their sheaths were ligated.

In Case 7, the delayed onset of the syndrome of acute central cervical spinal cord injury could scarcely have resulted from cervical cord oedema so long after the injury, and one must therefore consider the possibility of a traumatic thrombosis in the anterior spinal artery simulating the " late apoplexy " seen in traumatic cerebral lesions. There may be another alternative. The patient in Case 7 was psychotic; it is conceivable, therefore, that he could have suffered one injury which was followed by another episode of unwitnessed trauma some hours later, which accounted for his neurological signs.

Treatment

Lumbar Puncture.—This procedure should probably be used in almost all cases of spinal cord injury, and yet it is surprising to note how infrequently it is performed. The usual reason given for omitting the test is the fear of injuring the patient in manipulating him into a proper position for inserting the needle.

In our series of 12 patients, six had lumbar punctures. In the three hyperextension injuries which showed hypertrophic arthritis and in which spinal taps were made, there was no evidence of any block when the jugular vein compression test was done. This fits well with the data collected from our original series of nine cases in which there were four similar hypertrophic arthritis cases none of which involved subarachnoid space block. In the publication (Schneider *et al.*, 1954) in which we reported these cases, it was suggested that there were several points of compression or " squeeze " of the cervical cord, distributing the oedema of the cord over several segments rather than localizing it at any single given point. This meant that one of the important criteria for operation, namely, complete subarachnoid block, was lacking.

In the remaining six patients of the series presented above, who may have sustained a cord injury associated with compression fracture or fracture-dislocation of the cervical spine, three lumbar punctures were made. In two of them there was no block when the jugular vein compression test was carried out. (The patient in Case 7 had sustained a " crown type " compression fracture, and the individual in Case 8 had multiple compression fractures and " step " fracture-dislocations with multiple points of cord " squeeze ".) One patient in this group (Case 10) showed a straightforward fracture-dislocation of C_5 vertebral body anteriorly on C_6. He had a complete block on manometric testing. It is interesting to note the examiner's observation: " Thirty minutes after the application of the cervical traction, there was complete return of sensation." One wonders whether repeated hourly taps would not have demonstrated a release of pressure and oedema and a subsidence of the complete block. This may have occurred in Case 11, where the fracture-dislocation was reduced early. Since the operative indication of complete block was present in Case 10, no chances were taken and the patient was treated by decompressive laminectomy. He subsequently made a fairly good recovery, but the question must be raised as to whether this would have happened if operative intervention had not been employed.

Myelography.—This test was undertaken only in Case 1. It is mentioned again here only to emphasize the danger of the procedure. Since it is always necessary to hyperextend the cervical spine in order to prevent the flow of radio-opaque material into the skull, there is a danger of increasing spinal cord damage, for it is in the hyperextended position that the original injury occurs.

Operation.—The usual criteria presented for early operation upon patients with acute spinal cord injuries are complete block (as shown by the jugular vein compression test), an increase in neurological signs, or debridement of a compound fracture. In the majority of cases, and particularly in those where hypertrophic cervical spurring without fracture or dislocation of the cervical spine was found, these criteria were not present. In these individuals, anterior and posterior compression of the spinal cord existed simultaneously at several sites, so that no single point of spinal cord oedema or haematomyelia occurred and no subarachnoid block was usually to be observed. Damage to the cervical cord was acute. There was no progression of neurological signs but rather a regression, so that another of the customary indications for operation was absent. In the first patient discussed in our original presentation of this syndrome (Schneider *et al.*, 1954), surgical intervention actually created a further compromise of the lateral cortico-spinal tracts which had already been damaged. When pressure was applied gently in order to retract the spinal cord, to section the dentate ligaments, and to explore anterior to the cord, the lower extremity components (which lie laterally in the pyramidal tracts) were pressed upon, and the lower limbs, which the patient had moved pre-operatively, were paralyzed after operation. Conservative treatment is the most satisfactory in patients with acute central cervical cord injury. These people may be placed in some type of traction applied directly in the plane of the body until the spinal cord oedema has subsided. This usually requires about four weeks, at the end of which time a collar may be substituted for the traction apparatus for a period of another six to eight weeks.

A single point of " squeeze " of the cervical spinal cord is frequently found in patients with an acute central cervical cord syndrome after flexion injury with fracture-dislocation of the cervical spine. A complete block on the jugular vein compression test is more apt to be found in such patients than in those who incur the syndrome in hyperextension. Such a situation occurred in Case 10, where there was a complete block, and immediate operation was therefore indicated. No lumbar puncture was made in Case 9, because the patient's generally poor condition precluded operation even though a block had been found. With the degree of fracture-dislocation shown radiologically, a complete block might certainly have been present. Patients who demonstrate the acute central cervical cord injury syndrome with associated fracture-dislocation need immediate operation, therefore, only if a subarachnoid block is found when the jugular vein compression test has been made. Otherwise, cervical skeletal traction should be applied in an attempt to reduce the deformity, and this should be followed by a spinal fusion some weeks later, after spinal cord oedema has subsided.

Myelotomy has been advocated in acute traumatic haematomyelia by Elsberg (1941), Holmes (1915), Cohn (1931), and others. Allen (1911), in one paper, and Freeman and Wright (1953), in another, have presented experimental evidence of symptomatic improvement in animals with cord contusions when pial incision and dorsal myelotomy was performed.

The present authors are inclined to agree with Frazier (1918). He had observed that in traumatic haematomyelia there were numerous haemorrhagic zones in the spinal cord which were not necessarily in continuity. Thus, myelotomy would damage an oedematous, but otherwise normal, spinal cord. McVeigh's (1923) observations, made on the basis of his experimental work on traumatic haematomyelia, tend to support Frazier's thesis of multiple areas of haemorrhage and destruction in the spinal cord.

Prognosis.—In the patients who show the acute central cervical spinal cord injury syndrome, the prognosis is usually good. As the cord oedema subsides, recovery follows the pattern described above. Power in the lower extremities returns first, bladder function in the upper extremities next, and finger movements last. If central destruction of the spinal cord is marked, only partial recovery may result. Any residual neurological deficit is most often present in the upper extremities with most marked impairment in finger movement.

The mere quiver of movement of a single muscle or the presence of deep reflexes in the lower extremity in spite of an otherwise complete motor and sensory loss has enabled the authors to give a guarded but reassuring prognosis to the family. They may be told that there is a fair chance of recovery of motor power in the lower extremities and perhaps even complete recovery of the entire body as well.

Summary

Twelve cases of the acute central cervical cord injury syndrome have been presented in detail. One of these cases affords the first pathological confirmation supporting the assumptions previously made relative to the syndrome. The importance of accurate diagnosis is stressed, with emphasis placed on the fact that operation is contraindicated, that the prognosis may be good, and that should recovery occur it will follow a definite pattern.

Any paper of this type, which embraces compilation

of data from many sources, cannot be written without the cooperation of many individuals and allied hospital services. In the present instance, these include orthopaedic and radiology services as well as the neurosurgical. The authors wish to express their appreciation to the several staffs of the hospitals which aided in this work. In particular they are grateful to Dr. Will Glas, Department of Surgery, Wayne County General Hospital, for the opportunity of presenting cases from that institution. The authors also wish to thank Drs. James Hall and Adam McClay, of Munson General Hospital, Traverse City, Michigan, who have graciously supplied them with case material.

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THE MAY (1958) ISSUE

The May (1958) issue contains the following papers:—

The Neuropathy of Multiple Myeloma. Maurice Victor, Betty Q. Banker, and Raymond D. Adams.

The Relapsing Course of Certain Meningiomas in Relation to Pregnancy and Menstruation. Edwin R. Bickerstaff, J. M. Small, and I. A. Guest.

A Case of Intramedullary Neurinoma. B. Ramamurthi, V. C. Anguli, and C. G. S. Iyer.

Recurrent Multiple Cranial Nerve Palsies. Sir Charles Symonds.

Finger Tremor in Tabetic Patients and its Bearing on the Mechanism Producing the Rhythm of Physiological Tremor. A. M. Halliday and J. W. T. Redfearn.

Sensory Nerve Action Potentials in Patients with Peripheral Nerve Lesions. R. W. Gilliatt and T. A. Sears.

The Psycho-galvanic Reflex: A Comparison of A.C. Skin Resistance and Skin Potential Changes. J. D. Montagu.

Clinical Aspects of Susceptibility to Menthylpentynol. Edward Marley and Allen A. Bartholomew.

An Investigation of the Rosenow Antibody Antigen Skin Reaction in Schizophrenia. W. P. Gurassa and H. H. Fleischhacker.

Multilocular Cystic Encephalopathy of Infants. L. Crome.

Book Reviews.

A number of copies are still available and may be obtained from the Publishing Manager, British Medical Association, Tavistock Square, W.C.1, price 17*s.* 6*d.*

J. Neurol. Neurosurg. Psychiat., 1958, **21**, 228.

PROCEEDINGS OF THE SOCIETY OF BRITISH NEUROLOGICAL SURGEONS: 57th MEETING

The 57th meeting of the Society of British Neurological Surgeons was held in Holland as a joint meeting with the Netherlands Society of Neurosurgeons. Meetings were held at St. Ursula Clinic, Wassenaar, on May 9, and at the University Neurosurgical Department, Utrecht, on May 10. The two Presidents, W. R. HENDERSON (Leeds) and H. VERBIEST (Utrecht), occupied the chair in rotation.

Observations on Compression and Functional Recovery of Nervous Tissue

In 1936 A. C. DE VET (Wassenaar) reported a number of clinical observations which seemed to suggest the existence of a special form of pressure transmission in the intracranial contents. This mechanism differed from that associated with a general rise of intracranial pressure and seen in most space-occupying lesions.

Homolateral symptoms and signs occurred in 12% of intracranial tumours (Kernohan and Woltman, 1928); it was generally accepted that they were caused by displacement of the pes pedunculus against the contralateral sharp edge of the tentorium (Magnan, 1878-79; Collier, 1904; Purves-Stewart, 1927; Groeneveld and Schaltenbrand, 1927; van der Drift, 1957). Such signs were based on a different mechanism and should not be considered as caused by tentorial herniation.

Homolateral affections of the basal nerves, especially the fifth, were most often seen in lesions situated in the upper parts of the cerebral hemispheres and were due to downward displacement of the hemisphere on to the skull base. This syndrome was seen most often with extracerebral lesions, such as meningiomata, haematomata, and so forth, and less often with intrinsic brain lesions. The reason for this was that intrinsic lesions, surrounded by soft brain tissue on all sides, exerted pressure in all directions and consequently the pressure in one direction was less than in the case of a meningioma which was fixed against the skull on one side and exerted considerable pressure towards the brain.

A mechanism similar to that of crus pressure was seen in the case of sphenoidal wing meningiomas which displaced the optic nerve against the opposite edge of the optic foramen and so caused a temporal hemianopia.

The mechanism of producing symptoms in the Morgagni-Morel syndrome was considered in some detail. It was considered that the hypertrophic bone in the frontal region not only damaged the underlying frontal lobes of the brain but also, by exerting downward pressure, damage was inflicted on the diencephalic portions of the brain by counter pressure against basal structures, bone or dura. It was suggested that this mechanism accounted for the symptoms of mental and endocrine disturbance and of involvement of basal nerves.

The case history of a patient was presented who had a hyperostosing meningioma of the left fronto-parietal region. He also suffered from left-sided trigeminal neuralgia which seemed to be of classical type. Removal of the tumour was followed by recovery of the trigeminal neuralgia. It was suggested that the neuralgia had been caused by counter pressure of the skull base against the trigeminal nerve.

It was stressed that symptoms caused by such chronic *contre-coup* mechanisms often suggest a localization of disease quite different from that of primary tumour and this may lead to faulty treatment. The value of electroencephalography in localization was stressed.

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The Treatment of Prolonged Unconsciousness after Head Injury

A. v. d. ZWAN (Groningen) described a method of treating patients with prolonged unconsciousness and decerebrate rigidity after head injury. Only those cases with decerebrate rigidity were selected and comprised 11 patients. Unconsciousness in these cases was not very deep and seemed like normal sleep in contrast to lesions of the medulla which appeared to produce much deeper coma. The outstanding feature of the cases was decerebrate rigidity and mid-brain convulsions so that it was considered reasonable to treat them in the same way as status epilepticus.

Sedation was achieved with luminal or somnifane and when this was insufficient pentothal anaesthesia was used (eight cases). It was noted that experimental decerebrate rigidity in animals, produced by ligation of the carotids and basilar artery near the posterior cerebral, only appeared when anaesthesia had worn off.

Bronchial hypersecretion, so common in these cases, appeared to be reduced by this treatment and tracheotomy was required in only two cases. One of these had multiple rib fractures and a collapsed lung and the other was a late case admitted three weeks after injury from another hospital.

If patients did not improve, or deteriorated, then exploratory burr holes were made. In five cases this operation disclosed a subdural collection of fluid over the whole surface of the brain. This fluid usually had a high protein content but was, nevertheless, considered by Professor Booy (The Free University, Amsterdam) to be cerebrospinal fluid. It was not thought to be equivalent to a subdural haematoma but to be a fluid collection all over the brain similar to those described by McConnell and Phillips at previous meetings of the Society. Such a transudation from the brain surface after head injury had been described by Luyendijk at a recent meeting of the Dutch Society. An interesting feature of the cases was that air pictures consistently failed to show any evidence of air in the posterior fossa.

All the patients survived. One remained unchanged and though he developed a sleep-wake mechanism no verbal contact was possible. Two cases were left demented and with gross neurological abnormalities but were attending a rehabilitation centre. One patient, although seriously demented and with a right spastic paresis, was able to earn his living. Of the remaining seven cases, one had only transient unconsciousness for 18 hours, and the other six were able to return to a normal life, one having tremor of the right arm and one being slightly demented.

In considering the pathogenesis of cerebral lesions after injury it was suggested that, although stretching and tearing of nerve fibres was probable (Strich, 1956), anoxia might also play a considerable part. Anoxia could occur during the period of shock and was probably present during mid-brain fits also in spite of the deep and rapid respirations. In this connexion it was noted that chlorpromazine therapy had been abandoned since it was known that this substance, even in low dosage, lowered the resistance of the mid-brain to stagnant anoxia.

It seemed possible also that brain movement during injury might result in stretching of vessels in the circle of Willis and subsequent vasoconstriction. The value of pentothal anaesthesia in producing vasodilatation during angiography was well known and perhaps this method of treatment played a valuable part in helping patients over a critical period.

It appeared that decerebrate rigidity was more often seen in children than in adults, and that their chances of recovery were greater. If stretching and tearing of nerve fibres was the cause of the lesion, then one might refer to the lesion in children as a " green-stick " fracture of the brain-stem.

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Extradural Haemorrhage

Norman Whalley (Swansea) reviewed the findings—clinical and operative—and the end-results of 30 cases of extradural haemorrhage treated in the Neurosurgical Unit at Morriston Hospital, Swansea, during the period 1951-56. In this period 900 cases of injury to the head were admitted to the Neurosurgical, Traumatic, and Paediatric Units. The incidence of extradural haemorrhage was, therefore, 3·3%. Five of the patients died, the recovery rate being approximately 82%. Twenty-two patients were adults; eight were children of 12 years and under. Eighteen of the 22 adults recovered; seven of the children recovered.

In five cases there was no latent period. The average latent period in 25 cases was 11 hours. On admission to the Neurosurgical Unit, two-thirds of the cases showed alteration in consciousness together with pupillary changes. A similar proportion showed frank neurological abnormalities in the limbs. Five were in a state of decerebrate rigidity. Bradycardia was not a prominent feature in this series; it occurred in only eight cases. Only two patients presented with Jacksonian epilepsy.

Twenty-nine of these haemorrhages were localized accurately by the position of local scalp bruising. Fracture of the skull was present in 23 of the 30 cases; these fractures were seen either on radiographs or at operation. It was unusual to have other serious injuries in association with this condition. One patient had an injury to one optic nerve; another patient had a peripheral facial palsy; a third patient had a crush fracture of one dorsal vertebra without paraplegia.

Fifty per cent. of the haemorrhages were in the classical site in the temporal region.

The source of haemorrhage was found to be from the middle meningeal artery or its branches in 25 cases. In four cases bleeding came from the large venous sinuses (sagittal or lateral); in one case bleeding came from diploic channels at the fracture site.

The five cases which died were analysed in some detail. The first death occurred in a baby of 18 months. It was considered that death in this case was largely due to delay in starting a blood transfusion. The second death occurred in a young man of 22 years. He was transferred 24 hours after injury in a condition of decerebrate rigidity. A lumbar puncture had been performed immediately before his transfer and this was thought to have precipitated a tentorial pressure cone. The third death occurred in a man of 20 years. This case was transferred late and died in the ambulance. This patient was not operated upon. This patient also had a lumbar puncture before his transfer and this was thought to have precipitated tentorial herniation. The fourth death was in a man of 47 years who was transferred 48 hours after the injury. In this case there was also a small subdural haematoma. This patient had also been subjected to lumbar puncture but in this instance it did not result in tentorial herniation. It was felt that earlier operation would have resulted in recovery as there was no intrinsic brain damage apart from a small, superficial laceration of the temporal lobe. The fifth death occurred following a lumbar puncture. This was a man who had suffered from infrequent attacks of epilepsy for two years. More recently he developed headache and was admitted for investigation. There were no abnormal neurological signs and only slight blurring of the optic nerve heads. Following lumbar puncture a cerebellar pressure cone developed and the patient died within a matter of minutes. At necropsy an extradural clot was discovered in the posterior fossa. There was no fracture to be seen on radiographs and no fracture found at necropsy. Afterwards the relatives remembered that the patient had

fallen out of bed during an epileptic attack 14 days before his admission, striking his head. No other lesion was found.

All the 25 survivors returned to work in jobs, in the home, or at school. Two patients died later; one four years later from pneumonia. This patient was the only one in the series who developed epilepsy. The second patient who died later developed a cerebral tumour two years after the operation for removal of the extradural haemorrhage.

The remaining 23 were all working. Two had permanent homonymous hemianopias. These were considered to be due to infarction of the occipital lobe secondary to kinking of the posterior cerebral artery over the sharp edge of the tentorium in the production of the tentorial herniation.

It was stressed that the diagnosis of extradural haemorrhage was essentially a clinical diagnosis. Lumbar puncture was an extremely dangerous procedure if there was the slightest possibility of surface clot compression of the brain. Radiographs of the skull were useful only if they could be obtained quickly; delay for any reason jeopardized the chances of survival. Local scalp bruising was one of the most valuable localizing signs.

Local anaesthesia was the method of choice when operating; any procedure which increased venous congestion of the brain might precipitate tentorial herniation. Unilateral dilatation and fixation of a pupil, while a valuable lateralizing sign, was invariably a late sign and one of danger, indicating that speedy measures would have to be taken to relieve pressure on the brain-stem. It was of the utmost importance to provide blood transfusion, particularly in young children.

Atlanto-axial Dislocations

C. H. LENSHOEK (Groningen) presented the clinical, radiological, and operative features in 11 cases of atlanto-axial dislocation. These were divided into three groups.

The first group comprised six cases of traumatic dislocation with fracture of the odontoid. Two were in children of 5 years, the remainder adults. In the two children there was an epiphysial separation with forward dislocation of the atlas together with a Jefferson fracture of the atlas in two cases. Neurological complications were present in two cases, one of them severe. Treatment consisted of immobilization alone, skull traction followed by plaster, and in two cases spinal fusion.

The problem of traumatic subluxation was discussed briefly.

The second group consisted of two cases of non-traumatic acquired dislocations. One case was that of a 12-year-old boy with rheumatic arthritis; neurological signs were absent and spinal fusion was performed. The second case was that of a 75-year-old woman with cervical spondylosis and a quadriparesis who was treated by spinal cord decompression.

The third group consisted of three cases of occipitalization of the atlas with subluxation of the odontoid. Physiological and pathological movements of the odontoid were discussed briefly. Treatment consisted of decompression in two cases and decompression and fusion in the other.

Surgical treatment in this series was mostly carried out with the patient in the sitting position.

Endaural Hernia Cerebri

PETER H. SCHURR (London) presented the case histories of four patients with endaural cerebral hernia. He noted that cerebral hernia was one of several conditions, once relatively familiar and now becoming rare. However, a cryptic form still occurred occasionally which was the more important because of the readiness with which it responded to treatment. In this form there was an endaural prolapse of brain tissue through the roof of the ear cavity after mastoidectomy which, though sometimes visible at the auditory meatus, might only be visible on auriscopy or after dividing a false membrane which sometimes formed across the area.

Case 1.—F.H., a man, 48 years old, had chronic suppurative otitis media. During an endaural mastoidectomy the dura of the middle fossa was torn. Recovery was uneventful but the ear continued to discharge. Six months after the operation a pulsatile swelling was seen in the aural cavity. During the next six months it grew large enough to be seen at the meatus, after which it diminished in size. During this time the discharge continued. Craniotomy revealed an opening in the dura through which the brain had herniated. This was covered with fascia lata, after which the endaural swelling disappeared and the discharge ceased.

Case 2.—B. H., a woman, 29 years of age, had suffered from otitis media seven years previously for which a radical mastoidectomy had been performed by the post-auricular route. An offensive discharge returned and continued intermittently despite treatment. Further explorations were made following the development of temporal lobe epilepsy, headache, and temporal pain. Finally after dividing a web crossing the mastoid cavity, an endaural cerebral hernia was seen. This was repaired with temporal fascia through a craniotomy, following which the swelling disappeared, the fits almost ceased, and the remaining symptoms cleared up.

Case 3.—R.S., a man, aged 54 years, suffered a persistent aural discharge after a radical mastoidectomy and destruction of the labyrinth. A pulsatile swelling was seen in the roof of the cavity and repaired by Mr. Julian Taylor, who used a similar technique. Two months after the operation the protuberance had gone.

Case 4.—M.A., a 15-year-old girl, with a seven-year history of otorrhoea, had an endaural modified radical mastoidectomy performed. Convalescence was uneventful until eight months after the operation when a swelling appeared in the ear cavity and increased in size until it eventually filled the meatus. This was followed by cerebrospinal fluid otorrhoea and headache. Mr. Julian Taylor repaired the hernia in the floor of the middle fossa by closing the defect with fascia lata. The swelling diminished in size after this operation but returned and, at a second operation by Mr. Bernard Harries, a further small hole was found and occluded with muscle. Following this the swelling disappeared.

These relatively small endaural hernias might, therefore, be associated with persistent purulent discharge from the ear, cerebrospinal fluid otorrhoea, headache, and epilepsy—the latter in the absence of any previous history of abscess or generalized meningitis. A case in which a

similar condition followed fracture of the skull base had been described by Andrew (1951). There might be no clinical evidence of intracranial infection or raised pressure in these patients. The dura usually formed a collar around the hernia and seldom covered the protrusion (Caboche, 1902). Repair should be undertaken through a craniotomy and, when the defect in the dura had been exposed by division of the surrounding adhesions, the area should be widely covered with fascia on the intradural surface.

(He expressed his indebtedness to Messrs. Julian Taylor and Bernard Harries for permission to report Cases 3 and 4. Case 3 was also under the care of Mr. C. S. Hallpike.)

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Post-herpetic Neuralgia

W. Noordenbos (Amsterdam) reported the results of some investigations into this condition. The detailed results and conclusions are to be published at a later date.

Ventriculo-jugular Anastomosis in the Treatment of Infantile Hydrocephalus

T. B. Sikkens (Groningen) gave a preliminary report on a technique for making a shunt with a pump system between the lateral ventricle and superior vena cava in the treatment of hydrocephalus in infants. He noted that existing methods of treatment, such as shunts to the pleura or peritoneum, were unsatisfactory; removal of the choroid plexus and Torkildsen drainage operations often fell short of expectations and arachno-ureterostomy not only demanded the sacrifice of a kidney but also resulted in a continuous loss of electrolytes and cerebrospinal fluid. Direct drainage of cerebrospinal fluid into the venous system seemed to be the more physiological system to use.

Previous attempts at such a shunt had failed owing to back-flow of blood into the ventricular system and venous thrombosis. More recently, however, the construction of a shunt with a valve mechanism had been suggested and Nulsen and Spitz (1951) had reported a case treated by this method. Although pressure in the superior vena cava was nearly always lower than that in the lateral ventricle, nevertheless, some mechanism of preventing back-flow was desirable.

His apparatus consisted of a No. 6 rubber catheter which was inserted into the lateral ventricle via a parieto-occipital burr hole. This was led down under the scalp and joined a repercussion valve. This consisted of a plexiglass tube, 1·5 × 0·5 cm., in which a small chamber was hollowed out and contained a stainless steel pellet of 1·5 mm. diameter. Movement of the pellet would close the tube at the ventricular end thus preventing reflux of blood, but allowed passage of cerebrospinal fluid at the other end. There remained the risk that if the flow of cerebrospinal fluid was very slow or stopped, blood might diffuse up into the valve and block the tube. This was overcome by adding a rubber pumping valve distal to the repercussion valve. It was arranged that the rubber pump lay over the mastoid process. This pump was then connected to an animal-tested polyethylene tube which was passed into the internal jugular vein which was then ligated. As this ligation stopped flow in the vein it was desirable that the tip of the tube should reach as far as the innominate vein or the superior vena cava. The polyethylene tube could then be kept patent by pumping cerebrospinal fluid through it. Pumping was started soon after the operation and carried out several times a day. The child's parents were instructed in the mechanism and, after leaving hospital, they carried out the pumping procedure daily.

So far six cases had been treated by this method. In two the results had been very satisfactory with a follow-up period of 10 months. In the other cases, the results had not been good. After studying the causes of the bad results he had decided to replace the polyethylene tube by a silicone-coated ivory tube. This would not only reduce the possibility of clot forming in and around the tube end but would also allow the position of the tube to be checked radiologically.

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Choroid Plexus Papilloma and its Relation to Hydrocephalus

Bernard Fairburn (Romford) presented a case of choroid plexus papilloma and discussed the relation of such tumours to the development of hydrocephalus. He noted that the association of hydrocephalus with papillomata of the choroid plexus had long been recognized. In two-thirds of the cases the tumour was in the third or fourth ventricle and obstruction was presumably the mechanism whereby the hydrocephalus was produced. In the remaining third, the tumour was in one of the lateral ventricles. It had often been suggested that over-secretion of cerebrospinal fluid was responsible in such cases for the ventricular dilatation but there was little objective evidence that this was, in fact, the operative factor.

Case Report.—A 15-month-old girl was treated for communicating hydrocephalus. A benign choroid plexus papilloma was found in the right lateral ventricle at necropsy and no other lesion was present which could have explained the hydrocephalus. The child presented with an acute rise of intracranial pressure. Posterior fossa exploration, carried out in the erroneous belief that there was a cerebellar tumour, gave very transient relief. Within two weeks the intracranial pressure had risen again and was not controlled by lumbar punctures and aspirations of the posterior fossa decompression. (These latter aspirations were followed by profuse leakage of cerebrospinal fluid along the needle-track for several hours.) Finally, continuous ventricular drainage was established through a catheter in the right frontal horn. During the three days that the catheter was *in situ* the volume of cerebrospinal fluid secreted was 500 ml., 400 ml., and 960 ml. respectively. The child showed clinical signs of dehydration during this period.

He concluded that the findings in this case appeared to establish the fact that papillomata of the choroid plexus did secrete very large quantities of cerebrospinal fluid and that this was the mechanism of associated hydrocephalus.

The Active and Progressive Nature of Certain Intracranial Herniations

J. M. SMALL (Birmingham) discussed the progressive nature of certain intracranial herniations. He noted that for centuries there had been interest in herniations of all kinds and their complications. Since the middle of the last century the knowledge that pupillary dilatation was associated with intracranial compression had been understood, but not until 1920 was the anatomy related to pupillary dilatation described. The passive nature of these intracranial herniations had been too easily accepted and their progression after release of compression ill understood.

Comparison was made between unilateral temporal compression with progressive coning and bilateral pupillary dilatation with mid-brain signs from vertical and polar pressure, showing this to be the difference between uncal herniation and descent of the mid-brain through the tentorial hiatus.

The progression of the tentorial cone syndrome with a low intracranial pressure following treatment of the initial compression was described and the value of tentorial division in such cases outlined.

Cases of impacted herniation beneath the falx were also described with expression of the need for division of the falx to free the persistent herniation.

Finally, the strangulation of tonsillar herniations was described in anomalies of the foramen magnum area with secondary vascular and compression changes in the stem.

A Case of Meningioma in the Left Lateral and Third Ventricles

M. WEERSMA (Rotterdam) discussed intraventricular meningiomas and presented the details of a personal case. He noted that such meningiomas were unusual in their lack of dural attachment and their incidence was low, Cushing and Eisenhardt (1938) reporting only 19 cases, Esbach (1943) 53 cases, all of the lateral ventricle, and Huang and Araki (1954) five cases.

Case Report.—Mrs. L. v. G., aged 54, came of a family with psychotic and psychopathic tendencies. The patient's mother had committed suicide. In July, 1957, she had many complaints which included fatigue, forgetfulness, and vague pains everywhere in the body. After an occasional attack of vomiting she complained of dizziness and she fell down while walking. She was admitted to the Department on September 17.

Examination showed bilateral papilloedema of two diopters, there was no impairment of visual acuity but a right homonymous hemianopia. Anisocoria was noted but pupil reactions and external ocular movements were normal. There was no nystagmus. A slight paresis of the right face, arm, and leg was noted and also some impairment of sensory perception on the right. All reflexes were present, there was no ataxia or Rombergism. There was moderate arterial hypertension of 210/100 mm. Hg.

Radiographs showed a calcified mass, about the size of a hen's egg, in the central area of the head, mostly to the left of the midline. Ventriculography showed dilatation of both lateral ventricles and deformity of the left ventricle. Angiography showed slight displacement of the anterior cerebral artery to the right and widening of the loop of the pericallosal artery with compression of the carotid siphon.

Operation was carried out on September 26, an approach being made to the tumour through the posterior parietal region. (It was noted that approach through the temporal region or by occipital lobectomy could also be used in these cases.) A highly calcified tumour (80 g.) was removed, the major portion being in the lateral ventricle but some portion of it lying in the third ventricle. Histological examination confirmed the tumour as being a psammomatous arachnoidal meningioma.

After the operation there was marked oedema and bulging of the flap and a continuous fever but this subsided after three weeks. Immediately there was a right hemiplegia and astereognosis, aphasia of the amnesticreceptive type, alexia, and acalculia. There was loss of ability to recognize words and letters and to discriminate between the right and left sides of the body as well as external objects. The hemianopia was unaltered. By persistent training there was steady improvement. The patient could now walk without a stick and function in the right hand was also improved. The aphasia had also recovered to some degree, though alexia was still present. Her mental state was not satisfactory, there being depressive and hysterical manifestations, part of which might be ascribed to her previous psychopathic personality. (It was noted with reference to the investigations of Goldstein (1943) that some reserve should be exercised in applying the term hysteria to patients with parietal lesions.)

Ventriculograms and arteriograms were now nearly normal and the E.E.G. showed rhythmic 7 to 8 c./sec. activity and delta activity in the left parieto-temporal region.

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Pre-operative Dyshydration in Patients with Space-occupying Intracranial Processes

H. VERBIEST (Utrecht) gave a preliminary report on some investigations into fluid and electrolyte changes in patients with intracranial space-occupying lesions. He noted that in the past few years there had been a growing interest in the significance of disturbance of body fluids in neurosurgical patients. Most reports, however, had been concerned with changes in fluid pattern following trauma or surgery. The present report was concerned with pre-operative fluid disturbances in chronically ill patients suffering from intracranial space-occupying lesions. The investigation covered the period 1955-57 inclusive and comprised 254 patients. Patients with unknown pathology or in whom investigations were incomplete had been excluded.

In this series pre-operative dyshydration occurred only in lesions involving the cerebral hemispheres, cerebellum,

and fourth ventricle and tumours growing within the posterior fossa; there was one exception. In patients with lesions of the cerebellum and fourth ventricle there was a higher incidence of dyshydration in the lower age groups. In lesions of the cerebral hemispheres, 88·5% of 61 dyshydrated patients were older than 45 whereas 59% of 99 normally hydrated patients were younger than 45.

There was no obvious relation between frequency of pre-operative dyshydration and the type of lesion so far as the posterior fossa was concerned. In lesions involving the cerebral hemispheres, the incidence was very high in intracerebral haematomas and glioblastoma multiforme, namely, 75% and 61% of cases respectively. The frequency of dyshydration was 50% in subdural haematomas, subdural empyemas, and cerebral abscesses. It varied between 30% and 40% in astrocytomas and metastases and was lowest (12%) in meningiomas.

Frequent vomiting was the main cause of dyshydration in processes involving the cerebellum and fourth ventricle. In processes involving the cerebral hemispheres several factors were operative. These were, in order of frequency, mental symptoms which occurred in 60 of 61 patients and might have been responsible for insufficient spontaneous drinking or absence of the urge to drink; disturbances in drinking of administered water occurred in 42 or 61 cases and frequent vomiting occurred in 21 cases.

In frontal and temporal lobe processes the frequency of dyshydration was 52% and 49% and in parietal and occipital lesions 22% and 25% respectively.

The main patterns of fluid changes were: hyperosmolarity, hyperosmolarity and haemoconcentration, and haemoconcentration without hyperosmolarity. Azotaemia was present in 25% of dyshydrated patients with lesions in the posterior fossa and 79% of those with lesions in the cerebral hemispheres. In the whole series of 82 dyshydrated patients, acid-base equilibrium was disturbed in 42 cases, 33 presenting acidosis and nine alkalosis of metabolic origin. In the presence of dehydration the renal compensation for these disturbances is impaired.

In most cases of posterior fossa tumour, the fluid balance could be restored pre-operatively. Surgery of supratentorial lesions in dyshydrated patients had a very high mortality of 63% compared with a mortality of 21% in those admitted with a normal fluid balance and 17% in those who had their fluid disturbances corrected before operation. Sudden death during fluid replacement therapy occurred in two patients.

(This paper will be published in full in *Archivum Europeum Neurochirurgiae*.)

Pathological Elements Appearing in the Urine after Cerebral Lesions

R. C. KRUYT (Utrecht) presented a report on urine examinations in 462 patients who had had a neurosurgical operation or a head injury. In 48 of these abnormal constituents were found, including red cells, casts, and protein. Red cells appeared up to 100 per field and protein up to 20 g./litre. These abnormalities appeared on the second or third day and persisted for five to 10 days. During this period the urea clearance was diminished.

In addition to these abnormalities 20 patients (50%) had glycosuria, 29 (60%) had a severe uraemia, and 33 (70%) showed abnormalities in salt metabolism, either a salt retention with diminished excretion in the urine or an inability to retain salt, a salt-wasting syndrome. Pre-operatively none of the patients had abnormal elements in the urine. Of the 48 patients, 40 had a supratentorial lesion and of these 29 (70%) had a lesion of the posterior orbital gyri. The remaining eight patients had a posterior fossa or high cervical lesion.

He noted that it was known that stimulation of the splanchnic and renal nerves produced a decrease of kidney volume with anuria and after stimulation the urine contained red cells and protein. Trueta had described a change in blood flow through the kidney after such stimulation in which the cortex became bloodless and the juxtamedullary region overfilled with blood (the Trueta mechanism or Oxford shunt). It was also known that puncture of the floor of the fourth ventricle produced polyuria, glycosuria, and increased salt excretion. Stimulation of the anterior hypothalamus had produced a decrease in urine flow which was abolished by denervation of the kidney. Microscopical examination showed tubular necrosis in these cases. Stimulation of the frontal lobes, especially of the posterior orbital gyri or area 13 (Brodmann), produced the Trueta effect in the kidney and at microscopic examination there was a lower nephron nephrosis. A lower nephron nephrosis had been found in two patients dying after electro-shock treatment and examination of the urine in a number of patients so treated had shown the presence of red cells, casts, and protein. After ventriculography, and especially after lumbar encephalography, protein and red cells had been found in the urine and there was a decreased excretion of urea and salt.

In the series reported none of the patients was in a state of shock of any duration. In five patients treated with A.C.T.H. the already existing urinary changes did not become either better or worse so that stress was probably not a deciding factor.

The high proportion of lesions in the posterior orbital gyri in this group suggested the existence of a specific influence of this region of the brain on blood flow in the kidney. That the stimulus was probably conveyed via the brain-stem and spinal cord was suggested by the urine changes in patients with posterior fossa or high cervical lesions.

Compression of the Spinal Cord in Kyphosis and Kyphoscoliosis

R. MALMROS (Aarhus) presented a series of cases with kyphosis and kyphoscoliosis and spinal cord compression. In the Department of Neurosurgery in Aarhus, 18 patients had been operated on for this condition in the period 1943-58. Of these, 11 had a severe paraplegia, four a light or moderate paraplegia, and three bilateral spasticity and paralysis of one leg only. The patients could be divided into two groups according to age, a younger group in which the kyphosis was in most cases due to congenital malformations of the spine and an older group with mainly adolescent kyphosis (Scheuermann). In two cases the kyphosis was due to an old tuberculous

spondylitis. Only the facts related to the younger group were presented.

He noted that compression of the spinal cord with paraplegia was rare in kyphoscoliosis, most authors having reported only single cases. McKenzie and Dewar (1949) collected 36 cases from the literature and added five of their own. However, in one of their cases compression was due to a fibrous band and syringomyelia was later demonstrated in another. More single cases had been reported since then.

In his series there were seven males and three females. The age distribution was: 8-9 years two cases, 13-15 years three cases, 17-18 years two cases, and 21-24 years three cases. The clinical picture was very uniform. The symptoms were slowly progressive, starting with a staggering gait due to increasing spasticity and ending in paraplegia. Diminution of sensibility over the trunk and legs occurred and was followed, usually later in the course, by sphincter disturbance in the form of precipitate micturition or, sometimes, urinary retention.

Paresis usually began in the feet and spread upwards. The course was one of slow progression so that within six to 12 months there might be complete motor and sensory loss but still relatively little sphincter disturbance.

Another characteristic feature of the disease was that there was no pain during its progression. There might be numbness and tingling in the legs but the root pain so often seen in patients with spinal tumour or spondylitis was absent.

Of the 10 patients, nine had severe paraplegia and were confined to bed. One had bilateral spasticity and paraplegia of the legs, moderate in one and slight in the other, but was able to walk. The duration of symptoms was two to four months in two cases, five to six months in three, and 12 to 18 months in five cases.

All patients were treated by surgical decompression. An extensive laminectomy was performed at the apex of the kyphosis. The dura was found to be displaced anteriorly in the spinal canal and in eight patients there was a space between dura and laminae, 12 to 20 mm. wide, which was filled with fatty tissue. The dura was opened longitudinally and, as the cord prolapsed into the incision, transverse cuts were made and the edges sewn up.

Seven patients made a complete recovery (follow-up periods one to 13½ years). In three cases, the results were poor. One boy of 17 did not improve and died two years later. One boy of eight improved at first but symptoms recurred five years later. Re-operation six years after the original operation revealed extensive scar formation and adhesions in the spinal canal at the apex of the kyphosis. He was still living but with a severe paraplegia. The third case, a boy of nine years of age, had improved only slowly over a period of two years.

He concluded that cord compression was due to pressure exerted by the dura. This was bent over the kyphosis and behaved like an inelastic tube. The posterior dura approached the anterior dura and the cord was squeezed between.

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Radiological Aspects of Functional Listhesis of the Spine

P. HANRAETS (Wassenaar) discussed the radiological appearances of a functional form of spondylolisthesis. He mentioned the occurrence of apparent retroposition of a vertebra due to congenital antero-posterior shortening of the body and concave posterior margin to the sacrum but did not discuss these in detail. In a group of patients true spondylolisthesis with lysis of the arch occurred in 4%, pseudo spondylolisthesis with no lysis of the arch but disc narrowing in 6%, and functional listhesis in 7%. In this latter group certain mechanisms came into operation which disorganized the function of the lumbar spine so radically that listhesis might ensue, irrespective of whether the intervening disc had degenerated or not. The cause of listhesis appeared to be disease at levels other than at which displacement occurred. Indeed, the very existence of listhesis might not be suspected unless spinal function was examined radiologically.

This condition occurred when the spine was inadequate functionally with the result that the lumbar region was strained and the discs and ligaments put under such strain that, in order to provide the required curvature, vertebral bodies began to slip in relation to each other. One in every four of such minor displacements was multiple.

In this group of functional listhesis the causative factors found were: the latter months of pregnancy; a pendulous abdomen; chronic postural anomalies elsewhere in the spine such as thoracic kyphoscoliosis; a wide angle between lumbar spine and sacrum; any chronic back strain. Displacements in this group were more prone to occur in the presence of asthenia, a previous extensive laminectomy and dystrophia musculorum progressiva.

The extent of displacement might be only a few millimetres and not apparent for some time yet produce symptoms due to the effect of opposing forces. This was the probable mechanism of low back pain in the overstrained weak back. The beneficial effect of rest was due to the opportunity given to muscles to recuperate and so prevent the functional listhesis from coming into operation.

A second mechanism producing functional listhesis was any local area of fixation in the lumbar spine. Local limitation of movement had to be compensated for at other levels by vertebral displacement and this usually took place one segment above the fixed area. Where possible the displacement took place in an area where the strain was greatest, *i.e.*, one segment above, and at a place where the spine was most mobile. The discs were normal in the affected area and not primarily degenerative. This mechanism had been seen in association with the following conditions: Trauma at thoraco-lumbar level; disc herniation at high lumbar level; congenital synostosis of two lumbar vertebrae with long sacrum and transitional vertebrae; after disc operations and fusion operations and after infection; and in functional synostosis with disc herniation associated with muscle spasm and obliteration of the normal lumbar lordosis.

Low back pain in this second group was brought about primarily by the effect of opposing forces though root symptoms might also occur at a later date.

Every such displacement limited space relatively though it need not necessarily cause symptoms or signs. Their occurrence depended both on the degree of displacement and on the existing space within the canal. The coincidence of a functional listhesis with wide but oblate shape of the spinal canal in the lumbo-sacral region was mentioned. Such a shaped canal was a manifestation of a constitutional type and not identical with the wide canal seen in the thoracic and high lumbar regions (Elsberg, Dyke, and Brewer, 1934; Jefferson, 1955). The combination with spina bifida might be pertinent though a predisposition to relative stenosis had not been described (Walker, 1944). It might be inferred that the vertebral column with wide flat canal is predisposed to functional listhesis and where the two exist together the stenosis might be such as to effect root compression.

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Hyperthrophic Cervical Pachymeningitis in Three Sisters

M. P. A. M. DE GROOD (Tilburg) described the occurrence of cervical pachymeningitis in three sisters. They were the first, fourth, and eleventh children of a large family of 18. Symptoms and signs appeared in adult life and comprised a spastic paraparesis with claw hands. Sensory and sphincteric disturbances were absent in two of the cases. They all exhibited evidence of a dysraphic state with many congenital anomalies. These included dwarfism, short straight neck, broad face, high scapula, high palate, and kyphosis. Two sisters had a congenital systolic murmur in the heart and the third a mitral stenosis. Congenital narrowing of the cervical canal was excluded by radiography and myelography which showed, in all cases, a hold-up in the high cervical region. Operation was undertaken in each case and disclosed compression of the cervical cord by hypertrophic dura mater.

He noted that, although cases attributable to tuberculosis, syphilis, and trauma were recognized, idiopathic cases remained in which no cause could be found. Syringomyelia had sometimes been found in association. In the present group, as no other cause could be found, it was concluded that the hypertrophic pachymeningitis was a manifestation of the dysraphic state.

BOOK REVIEWS

Morphologie und Physiologie des Nervensystems. By P. Glees. (Pp. xii + 445; 149 figures. DM. 58.-.) Stuttgart: Georg Thieme. 1957.

This book by Dr. Glees will be a useful source of information to those who are studying the behaviour of the nervous system from whatever angle. Experimental neurology now covers a vast field in which anatomists, physiologists, psychologists, biochemists, clinicians, and many others are each cultivating their separate plots. Dr. Glees is one of the few people who try to study the landscape as a whole. Inevitably his description of each little field may disappoint those who work within its confines, and may be considered by them to be superficial or uncritical. And yet the general result is a valuable encouragement to the student to think widely and to know something of all that is going on.

This volume is well produced with some excellent diagrams and ample references at the end of each chapter. The cost seems to be excessive.

Handbook of Neurological Examination and Case Recording, revised edition. By D. Denny-Brown. (Pp. viii + 114. 22*s*.) Harvard University Press. (London: Oxford University Press.) 1957.

This admirable little book is the second edition of a concise but comprehensive guide to neurological examination. It contains much clinical information which is often not included or is difficult to extract from a larger textbook. It is therefore unfortunate that the high price of 22*s*. will prevent many students and younger doctors from possessing it, the more so when it is issued from the presses of two universities.

A Textbook of Clinical Neurology, 8th ed., with an Introduction to the History of Neurology. By I. S. Wechsler. (Pp. 782; illustrated. 77*s*.) Philadelphia and London: W. B. Saunders. 1958.

This textbook was first published 30 years ago. It is no easy matter to keep a textbook up to date and in this instance it would certainly have been better to start again. The information provided about many recent advances in knowledge is quite inadequate. Thus the reader will turn to these pages in vain to find out how to treat a case of meningitis, or how to investigate the metabolic abnormality in hepato-lenticular degeneration, and yet the method of giving malaria to cases of G.P.I. is still described. References to the handling of conditions such as cerebral abscess and subdural haematoma are clearly out of touch with modern surgical practice. It is astonishing to read that pachymeningitis haemorrhagic interna is still considered as a disease separate from chronic subdural haematoma, and that "the treatment is symptomatic" (p. 513).

The Mammalian Cerebral Cortex. By B. Delisle Burns. (Pp. vii + 119; 24 figures. 21*s*.) London: Edward Arnold. 1958.

The author of this monograph is well known for his experimental observations on the properties of isolated areas of cerebral cortex, and his critical assessment of the phenomena observed in this field of research form a most interesting part of this book. The prolonged response to a single stimulus, the burst response of isolated cortex, and other forms of after-discharge all give glimpses of neuronal mechanisms which are tantalizing in their complexity.

In discussing the possible explanations of some higher cerebral mechanisms he writes (p. 56): "It would be helpful to the average reader if the authors of papers on the upper end of the central nervous system were to state, before their section on methods, their prejudices and their hopes."

In a careful discussion of the spontaneous activity of central neurones the author practices his advice and admits a mild prejudice against the belief that there are cells within the central nervous system whose discharge is spontaneous. His final conclusion is that the existence of such cells has not been proved, and then with an almost peevish gesture, adds that the importance of this question has in any case been over-emphasized !

The last chapter discusses the possible mechanisms involved in memory and here the references to clinical observations are hesitating and not so authoritative. The earlier chapters will, however, be read eagerly by students of brain mechanisms.

La Therapeutique des Affections Vasculaires Cérébrales. Reports presented to the 31st French Medical Congress, Paris, 1957. (Pp. 190; 10 figures. Fr. frs. 1,800.) Paris: Masson. 1957.

This book is a collection of reports prepared for the thirty-first (1957) congress of French medicine and comprises seven papers dealing with the treatment of cerebral vascular disease.

The first paper, written by Professor Alajouanine and his colleagues, deals with the physiology of cerebral ischaemia and the pathology of cerebral haemorrhage, infarction, and oedema. Cerebro-vasospasm is apparently no longer acceptable to the French school of neurology but the conjectural possibility of spasm occurring in the internal carotid or vertebral arteries has to some extent replaced it as a causation of transient ischaemic episodes. The evidence for this seems to be the vasoconstriction seen during cerebral angiography.

The other contributions deal with the treatment of cerebral haemorrhage, of apoplexy in general, of cerebral arterial thrombosis, of cerebral thrombophlebitis and,

finally, with the surgical treatment of cerebrovascular accidents. Each paper has its own extensive bibliography and there are seven well produced carotid angiograms. Unfortunately there is no index.

The difficulty with a book of this kind is the amount of repetition that seems inevitable, because each set of authors naturally wish to state their views widely about the pathology and treatment of this difficult subject, and so considerable over-lap develops. Generally it seems that the French have abandoned stellate ganglion block for cerebral infarction, and are opposed to the use of anticoagulants in the acute attack except for cases of cerebral embolism. It is perhaps a little surprising to find this hesitancy to use anticoagulants in the paper on intracranial thrombophlebitis, where the only firm indication for their use is thought to be cavernous sinus thrombosis.

Routine cerebral angiography was performed in all cases of suspected cerebral infarction by the Toulouse school, and in 4,000 arteriographies only four cases were made worse.

There is the surprising omission from this book of basilar or vertebral arterial stenosis, and there is very little reference to cerebral embolism, although carotid atheroma is given due importance. Otherwise this volume gives a good idea of French opinion on cerebral vascular diseases and their treatment.

Villiger's **Die Periphere Innervation,** 11th ed. Edited by Eugen Ludwig. (Pp. 210; 20 figures. S. frs. 20.-.) Basel/Stuttgart: Benno Schwabe. 1957.

Ten years have elapsed since the tenth edition of Villiger's well-known compendium of the anatomy and pathology of the peripheral nervous system. Therefore, several parts of the book had to be rewritten to include new experiences, especially the chapter on the autonomic system.

The many editions prove the popularity this book has achieved by students in anatomy and neurology in the past, and the new edition will be welcomed.

Pathologie et Chirurgie des Carotides. By Georges Arnulf. (Pp. 544; 154 figures. Fr. frs. 6,000.-.) Paris: Masson. 1957.

This is an extensive study of the carotid arteries from a standpoint which is angiosurgical rather than neurosurgical. The first part is devoted to anatomy and physiology; the second to operations on the carotids, including chapters on grafting, jugulo-carotid anastomosis, arteriectomy, and intracarotid blood transfusion as a method of resuscitation; the third describes carotid pathology; and the fourth and last part, on the surgery of the carotid sinus and body, has a lot to say about denervation and infiltration of the carotid sinus for a variety of conditions.

The approach to the subject is that of the school of the late Professor René Leriche, at whose instigation the author, his pupil, undertook this study. Certain matters therefore receive an emphasis that might not be accorded to them in this country, but the authoritative character of the book is not lessened because of this. There are 83 pages of most valuable bibliography.

5-Hydroxytryptamine: Proceedings of a Symposium held in London, 1957. Edited by G. P. Lewis. (Pp. xv + 249; illustrated. 60*s*.) London: Pergamon Press. 1958.

This volume records the proceedings of an international symposium held at the Wellcome Foundation in April, 1957. Rapid progress has been made in this subject since it was shown that the enteramine of Erspamer and the serum vasoconstrictor of Page, Rapport, and Green were each identical with 5-hydroxytryptamine. The distribution of serotonin in nature, the biochemical mechanisms involved in its formation and destruction and its actions on the animal body are all considered in this volume. The contributors to this symposium have themselves been responsible for many of the major discoveries concerning serotonin and the volume is certainly the most comprehensive and authoritative summary of knowledge on the subject at present available.

It is not as yet possible to define the role of serotonin in the animal body and knowledge of its pharmacological actions exceeds understanding of its physiological functions. This is particularly true of the relation between serotonin and the functioning of the nervous system. The substance is present in brain; its distribution within the brain is very uneven and there is evidence that it is more rapidly synthesized and broken down in the brain than anywhere else in the body. Furthermore, drugs which profoundly affect nervous function, such as lysergic acid diethylamide, reserpine, and inhibitors of amine oxidase are known to react with serotonin in one way or another. It remains to be seen whether these various observations can be integrated in such a manner as to illuminate understanding of normal and abnormal nervous function.

Quantitative Untersuchungen an der Sehrinde. By Herbert Haug. (Pp. 130; 49 figures, 29 tables. DM. 15.-.) Stuttgart: Georg Thieme. 1958.

This book is a very praiseworthy attempt to give a more objective basis to the study of cytoarchitecture. Previous definitions of the various histological characteristics of the brain which have been published have often been based on little more than the personal authority of the author concerned. Haug on the other hand has now used the quantitative method elaborated by Chalkley to determine the volume of nerve cells and glia cells in the visual cortex of man and other mammals. Besides 20 normal human brains Haug also examined six schizophrenic brains and in these he found no statistically significant differences in the nerve cell or glia population, as compared with the normal brains. It appears that the duration and type of fixation is less significant in this type of quantitative analysis than one might have thought; certainly this is a fact which has not been evident in previous work of this kind.

The book contains a great deal of information on the quantification of brain cells, and Haug's approach to the problem is both careful and critical. His results are

illustrated by clear and instructive diagrams and the book should prove to be most useful to anyone who intends to make a quantitative study of the brain.

Experimentelle Beiträge zur Pathogenese der Commotio Cerebri. By F. T. Merei, Th. Hasznos, and E. Grastyan. (Pp. 128; 48 figures. Price not given.) Budapest: Akademiaikiado. 1957.

This monograph from Hungary first reviews the literature of experimental head injury and then describes the findings in 50 experiments performed on cats. Changes in the E.E.G. are recorded, and special attention is paid to the circulatory reactions and to the microscopic changes in the arterioles and capillaries. Those interested in experimental *commotio cerebri* will find this a useful book of reference.

Liver-Brain Relationships. By Ian A. Brown. (Pp. xiii + 198; 26 figures. 50*s*.) Springfield, Illinois: Charles C. Thomas. 1957.

This monograph is based on a study of 82 patients with hepatic disease, 40 of whom died in coma. The series was collected before 1953 and, almost inevitably with a rapidly advancing subject, certain newer techniques have not been available. Blood ammonia estimations and portal venography were seldom performed. The clinical sections are disappointing, as statistical lists of symptoms and signs are not an adequate substitute for clear descriptive writing. The neurologist will obtain little help in the management of the mildly demented and tremulous patient with abnormal liver function tests. The term " hepatoencephalomyelopathy " to describe the syndromes of nervous disorder secondary to liver disease is not likely to come into general use, particularly as evidence of involvement of the spinal cord is slight.

The value of the book lies in drawing attention to the potentially extremely varied ways in which disordered liver function may affect the brain. The metabolic functions of the liver are, however, so extensive, and the requirements of the brain so little understood, that an almost limitless field of speculation is opened. The review of biochemical data contains much valuable information and suggests many starting points for further investigation. The author's plea for intensive application of biochemical techniques to neurological problems is undoubtedly just, but is perhaps carried a little too far in his hope that this monograph " will signal the termination . . . to clinical correlative studies ". It is surely precisely in correlating clinical states with chemical data revealed by newer techniques that future advances must lie.

It remains to be said that the author does not employ the English language with felicity and that the price of the book might well be reduced by the omission of full-page portraits of Hippocrates, Galen, and Kinnier Wilson.

Der Suicid. By F. Dubitscher. (Pp. viii + 224; 7 figures, DM 16.50.) Stuttgart: Georg Thieme. 1957.

Dr. Dubitscher's thesis is that in turbulent times external stresses are far more important causes of suicide than intrapsychic conflicts. His evidence lies in the analysis of 3,208 cases of suicide occurring between 1938 and 1955 in soldiers or former soldiers of the German Army. Whereas in most studies of suicide certain factors have generally been found significant, *e.g.*, marriage, number of children, time of year, constancy of occupation, no such relationship could be detected in these men. Close study of their records suggested very strongly that circumstances peculiar to the conditions of war as experienced in Germany far outweighed personal difficulties which might have operated at other times. The political situation before and during the war, the abominable duties some of the men were called on to perform, their hardships, and the chaos that followed military collapse and invasion were evidently unmistakable determinants of the suicidal act. The monograph contains much statistical information and informative comment. The author is aware of the inevitable defects in his material, but gives a convincing and detailed presentation of the weight of misery which evidently drove these men to suicide. The book can be read not only as a socio-medical document but as a tract for the times.

The Analysis of Fantasy. By W. E. Henry. (Pp. 305. 48*s*.) New York: John Wiley. 1957.

It is over 20 years since Henry Murray described his thematic apperception test. It has passed through the normal vicissitudes of a " projective " personality test, like its elder sister the Rorschach ink blot. Less is expected of it than in its golden youth, and there are many who doubt whether it can tell us more about a subject's personality than can other varied samples of his verbal behaviour: interpretation is still too uncertain and dependent on the interpreter. Dr. Henry presents a sober and well organized account of the process of interpretation, as usually performed, followed by illustrative analyses, a study of the stimuli in each picture, and notes on the method of administration. There is also an ample bibliography. The chief defect of the book is that it does not examine the problems of validation: Dr. Henry, aware of this, hopes that he has provided a conceptual basis upon which studies of validity can be founded, but until an author has himself grasped the validation nettle he cannot claim to have guided his readers well through the thick undergrowth. It is a merit in this book that it keeps free of loose psychoanalytical speculation, focuses on the normal personality, and pays much heed to social and cultural influences.

Cerebral Palsy in Childhood. By Grace E. Woods. (Pp. xi + 158; 34 figures. 27*s*. 6*d*.) Bristol: John Wright. 1957.

This book consists chiefly of a clinical analysis of 300 children with cerebral palsy seen in the Bristol area. The pathological and physiological problems connected with this difficult subject are not given much consideration, nor are the problems of treatment discussed

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FURTHER OBSERVATIONS ON SUBARACHNOID HAEMORRHAGE

BY

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This paper is a direct sequel to that of two of the authors (McKissock and Walsh, 1956) in which evidence was produced to suggest that surgical treatment for ruptured intracranial aneurysm led to a lower mortality rate than the 50% which had been widely accepted as the death rate under conservative treatment. In that paper was collected a series of 108 cases of ruptured aneurysm treated medically during a period when surgical treatment was virtually not practised and in which the death rate was 50%. This was contrasted with a largely subsequent series of 141 patients subjected to surgical treatment with a mortality rate of 33·3%. That the two series were not strictly comparable must be conceded, for the patients were admitted during two different periods at a time when progressively greater interest was being shown in the conditions of subarachnoid haemorrhage and ruptured aneurysm, the techniques of angiography were improving, and the mode of selection of patients for transfer to a neurosurgical unit was changing.

Unfortunately the literature contains no report of a large unselected series of proven ruptured aneurysms treated by medical means alone so that there is no reliable figure for the death rate under these conditions against which the effect of modern surgical methods of treatment can be assessed. Magladery (1955) attempted to compare the results of medical and surgical treatment but his figures were unacceptable for an assessment of the death rate in cases of aneurysm for only 90 of the 235 cases were subjected to angiography and the series treated surgically was too small (37 cases) to be significant.

Of the many series of cases reported by surgeons in recent years none can be accepted as giving a correct picture, either because the material had been selected, the number of cases was too small, or the time of operation after haemorrhage was not given.

Norlén and Olivecrona (1953) were discouraged, for example, by a death rate of eight patients of 15 operated upon from a few hours to 22 days after the haemorrhage and concluded that operation should be delayed until the quiescent period of three to four weeks after the bleed when they demonstrated a death rate of only two patients of 63 operated upon. Such a series of 15 cases was too small upon which to dogmatize and a delay of three to four weeks permitted of too large a proportion of deaths from recurrent haemorrhage.

This present paper deals with 261 additional patients shown by angiography, operation, or necropsy to have suffered rupture of an intracranial aneurysm. The patients were admitted during the period April 1, 1954, to June 30, 1956, in which time 455 patients with subarachnoid haemorrhage were admitted to the Neurosurgical Department (Table I).

TABLE I

DIAGNOSIS IN 455 PATIENTS WITH SUBARACHNOID HAEMORRHAGE

	No. of Patients	No. of Deaths
Intracranial aneurysm	261 (57%)	120 (46%)
Intracranial angioma	26 (6%)	7 (27%)
Due to specific disease	2	0
Aneurysm and angioma	1	0
Cerebral or cerebellar haemorrhage	47 (10%)	33 (70%)
Unexplained subarachnoid haemorrhage	118 (26%)	12
Total	455	172 (38%)

Unexplained Subarachnoid Haemorrhage

The clinical importance of this group lies in the better prognosis which can be given when angiography has proved negative, for, of these 118, 83 have been followed for periods of six months to over three years with only 12 deaths, a mortality of 14%. It is important to note that 140 patients had negative angiograms, of whom 34 died, 22 of whom were found to have aneurysms at necropsy.

Intracranial Aneurysms

Our main purpose in this paper is to record the results of our management of the patients with ruptured intracranial aneurysms. In general we considered this condition an emergency and began investigations as soon as the patient reached our unit. After the usual careful history taking, neurological and general examination, the patient's reaction to compression of one and then the other carotid artery

in the neck for 10 minutes was tried. If the patient tolerated this procedure without any deterioration in the state of consciousness or the development of new neurological signs, bilateral carotid angiography was carried out forthwith. If the patient did not tolerate carotid compression, then angiography was delayed and during the following days increasing periods of carotid compression were carried out until the patient would tolerate the necessary 10 minutes, when angiography was performed. Operation, if indicated, was carried out shortly after angiography, usually within 24 hours of admission, although in certain circumstances operation was delayed for four or five days and occasionally for as long as two weeks. In the main we were concerned with treating all patients with ruptured aneurysms which were surgically accessible with the knowledge that there would be a high mortality and morbidity in patients operated upon soon after the bleed. We believed, however, that this would be lower than the natural mortality and morbidity. In our opinion early angiography was essential for, in the moribund patient, an intracerebral haematoma might be demonstrated and could be at once evacuated whereas in the others there was no means of knowing when a further, and possibly fatal, haemorrhage might occur.

There were 261 patients with intracerebral aneurysms, their anatomical distribution being shown in Table II. These figures corresponded closely with those of previous reports except for the higher incidence of patients with multiple aneurysms which might well be a reflection of improved angiographic technique and interpretation.

TABLE II

SITE OF RUPTURED ANEURYSMS

	No. of Patients
Anterior cerebral—anterior communicating	79 (31%)
Internal carotid—posterior communicating	58 (22%)
Middle cerebral	39 (15%)
Bifurcation internal carotid	24 (9%)
Posterior cerebral, basilar, cerebellar	8 (3%)
Distal anterior cerebral	6 (2%)
Others	3 (1%)
Multiple	44 (17%)
Total	261

Selection of Patients for Treatment

During the period covered by the admission of the 261 patients of this series the tendency was one of ever-increasing recourse to surgery whenever the aneurysm appeared amenable to such treatment. The reasons for withholding surgery were broadly these: (1) Death before investigation or before surgery could be undertaken; (2) failure to withstand carotid compression; (3) failure to demonstrate the lesion by angiography; (4) unsatisfactory cross-circulation as, for example, in anterior cerebral-anterior communicating aneurysms where the operation of choice was an appropriate proximal anterior cerebral clip; (5) a clinical state of akinetic mutism. Surgery would not be withheld because of the poor clinical condition of the patients, many of whom indeed were operated upon when *in extremis*.

Classification

The patients were classified in the same manner as in our preceding paper.

Category A.—This category included patients who were in danger of dying in the immediate future from the haemorrhage causing admission to hospital. It also included all those who were in coma or a semiconscious state with severe neurological signs.

Category B.—Patients who had completely, or in part, recovered from the haemorrhage resulting in hospital admission were seen within eight weeks of the last bleed, but were not in danger of dying from that initial haemorrhage. This category included patients in good general condition but who might or might not still show some residual signs of haemorrhage. They were still, however, at considerable risk from a further haemorrhage.

Category C.—These patients had recovered completely, or with residual signs in the central nervous system, from the initial bleed but were seen more than eight weeks after the haemorrhage.

In this category most patients were completely well and only a few had residual signs of the brain damage caused by the original haemorrhage. They, of course, were still at some risk from a further haemorrhage, but probably only to the order of about 20%.

Angiography

Two hundred and fifty-three patients had angiographic investigations and the aneurysm was demonstrated in 231 of these (91%). In those patients with more than one aneurysm not all of these in a particular patient were necessarily shown by angiography. In 22 patients the angiogram was negative and the lesion was demonstrated at necropsy or, rarely, at operation. Eight patients died before angiography was performed.

Results of Treatment of Intracranial Aneurysms

It is most important to stress the fact that all references to mortality indicate death at any time during the stay in hospital or the period of follow-up.

TABLE III

RESULTS OF TREATMENT (ALL ANEURYSMS)

	Category A		Category B		Category C	
	No.	Deaths	No.	Deaths	No.	Deaths
Untreated	41	36	39	17	5	0
Removal of clot	13	11	—	—	—	—
Exploration only	—	—	3	3	—	—
Carotid ligation	30	19	67	12	3	0
Intracranial operation	20	10	40	12	—	—
Totals	104	76	149	44	8	0

The gross results are shown in Table III. In Category A there were 104 patients, of whom 41 were untreated with 36 deaths (88%). The remaining 63 were subjected to some form of operation, of whom 40 died (63%).

In 13 of the patients the operation was confined to evacuating an intracerebral clot, sometimes because angiography had not been performed, 11 of whom died (85%). In 17 cases intracerebral clots were evacuated in conjunction with some other form of surgery and 13 died (77%). The overall mortality in patients requiring removal of a large intracerebral clot was thus about 80%.

Thirty patients had had a carotid ligation, of whom 19 died (63%), and 20 had had an intracranial operation and of these 10 died (50%).

There were 149 Category B patients and of these 39 (26%) were untreated with 17 deaths (44%) and 110 treated surgically with 27 deaths (25%). Some of the untreated patients in this group were only shown to have aneurysms at necropsy. Of the surgically treated group, three had had an exploratory craniotomy only and all three had died. In 67 a carotid ligation was performed and 12 died (18%). (" Carotid ligation " is taken to mean single or combined ligature of the three carotid vessels in the neck—common, internal, and external.) In 40 patients an intracranial operation was carried out and 12 died (30%). In Category B evacuation of an intracerebral clot was performed in conjunction with some other operative procedure in 15 patients of whom four died (27%).

In Category C there were only eight patients, five untreated and three treated by carotid ligation without any mortality.

Considering all cases, 85 had been untreated with 53 deaths (62%), and 176 had been treated surgically with 67 deaths (38%), 45 patients had had an intracerebral clot removed, in 32 cases with some other operative procedure, and 28 died (62%), 100 had had a carotid ligation in the neck with a mortality of 31 (31%). The mortality of 63 intracranial operations was 25 (40%).

Cause of Death

Cerebrovascular disease was considered to be the cause of death, though not necessarily the terminal disease, in 110 patients (92%). In four untreated cases and one surgically treated case death was due to an unknown cause—unknown because we had no clinical details of the mode of death in a patient who had died some time later having been discharged well from our unit. In five patients who were all surgically treated, the cause of death was unrelated to the cerebral condition or to the operation.

Time of Death

Death occurred within one month of the first haemorrhage or of operation, in 106 patients (88%), 11 died from one to six months after, and only three more than six months after the haemorrhage or operation. The longest survival to death was two years and five months after the subarachnoid haemorrhage which led to admission to our unit.

Influence of Loss of Consciousness at Time of Haemorrhage

Walton (1956) has shown that the prognosis is worse in patients suffering a coma-producing haemorrhage than in those in whom consciousness is not lost. In our patients a coma-producing haemorrhage occurred in 170, of whom 94 died (55%), whilst of 82 with bleeds not producing coma only 25 died (30%). Surgical treatment was denied to 60 patients with coma-producing haemorrhages, of whom 46 died (77%), whereas of 110 patients treated surgically, 48 died (44%). Surgery was withheld from 25 patients who did not lose consciousness as a result of the bleed, of whom seven died (28%), whereas 57 were operated upon with 18 deaths (32%).

The results in these groups treated with or without operation were not comparable, for non-surgical treatment might well have been due to death before investigation or before surgery could be undertaken.

The roughly comparable death rates in the haemorrhage cases without coma gave no indication of any superiority of surgical treatment.

Age in Relation to Mortality

Table IV shows the mortality in the series in relation to the age of the patient. It will be seen that

TABLE IV

MORTALITY IN RELATION TO AGE

	Untreated		Surgically Treated	
	No.	Mortality (%)	No.	Mortality (%)
Under 50 years	31	52	96	32
Over 50 years	54	61	80	45

for both the untreated series and the surgically treated series patients over 50 years of age did not fare so well as those under 50 years of age. When the figures were broken into decades it was seen that in the untreated group the mortality rose slowly with each decade, whereas the surgical mortality remained fairly constant until the age of 60 years and then rose rapidly in the older patients from approximately 35% below 60 to over 50% after 60 years. The proportion of patients operated upon was higher in the younger age groups and this might have been by natural selection—death—or rarely by conscious selection on the part of the physician or surgeon. Up to the age of 50 years 76% of patients were surgically treated whereas over 50 years only 61% were operated upon.

Blood Pressure in Relation to Mortality

Raised blood pressure was found to be an adverse factor in survival of patients after a subarachnoid haemorrhage. For our purposes the maximum normal level of blood pressure was taken to be 160/90 mm. Hg. and the pressure recorded on admission was accepted as the patient's usual blood pressure unless there was evidence of previous persistent hypertension when the patient was included as hypertensive.

In nine instances the blood pressure was not recorded. Six of these patients died (67%).

One hundred and fifteen patients had a normal blood pressure and 40 of these died (35%), 35 were untreated with 18 deaths (51%), and 80 were treated surgically with 22 deaths (28%). Five were treated by removal of intracerebral clot alone and all died, as did the two who had had an intracranial exploration. Forty-four patients had had a carotid ligation in the neck and of these seven died (16%), and 29 patients had had an intracranial attack upon the aneurysm with eight deaths (28%).

One hundred and thirty-seven patients were hypertensive and 74 of these died (54%). Forty-four had been untreated with 31 deaths (70%), and 93 treated surgically with 43 deaths (46%), eight had been treated by removal of clot only with six deaths (75%), and one, who also died, by exploration of the aneurysm. In 56 a carotid ligation in the neck had been performed with 24 deaths (43%), and 28 had had an intracranial attack upon the aneurysm with 13 deaths (46%).

In all instances, except for removal of an intracerebral clot, the hypertensive patient seemed to fare less well than the normotensive patient.

Time of Operation in Relation to Mortality

The mortality in those patients operated upon within three days of a haemorrhage was approximately 53%, from the fourth day to the end of the second week the mortality was about 33%, in the next four weeks about 19%, after which there was no death (Table V).

TABLE V

TIME OF OPERATION IN RELATION TO MORTALITY

Interval between Subarachnoid Haemorrhage and Operation	No. of Patients	Deaths	Mortality Rate (%)
Less than one day	44	25	57
Two days	13	6	46
Three days	14	7	50
Four to six days	26	10	38
Seven to nine days	15	4	27
Ten to thirteen days	22	7	32
Two to three weeks	14	3	21
Three to six weeks	18	3	17
Six to eight weeks	5	0	0
Over eight weeks	3	0	0

Recurrence of Bleeding after Treatment

There was evidence of recurrent bleeding after admission to our unit in 16 untreated patients, all of whom died. Thus, of 85 untreated patients, 37 had died from the haemorrhage that had brought them to the Neurosurgical Department. Of the 48 survivors, one-third had had a further haemorrhage which resulted in death. No cases are recorded of patients in whom haemorrhage recurred but not fatally, although some haemorrhages after discharge might have escaped our records.

Recurrent bleeding occurred in three treated patients in whom surgery was confined to removal of an intracerebral haematoma but only two of these patients died as a result.

Haemorrhage recurred in 14 patients after carotid ligation and in 13 cases death followed. This seemed a high figure and in many instances was dependent upon the pathologist's view that the haemorrhage in the subarachnoid space or brain was more recent than the haemorrhage before operation. In some instances certainly there was some doubt about this interpretation.

Four patients had had a further haemorrhage after a craniotomy with attack on the aneurysm.

Follow-up in Living Patients

Of the 141 survivors, 135 had been followed for more than six months, 121 for more than a year, 45 for more than two years, and six for more than three years. The possible follow-up and the percentage follow-up was: one-two years 141 (95%), two-three years 56 (80%), over three years 14 (43%).

Late Follow-up Results

The quality of the final result in the survivors was also of some interest when comparing the results of treatment.

Of the 32 untreated survivors, 25 were at full work, though some may have had minimal signs, two were partially disabled, and four were totally disabled and dependent. There was no follow-up in one patient.

Of the 109 survivors after surgical treatment, 76 were at full work, although some may have had minimal signs—69% compared with 75% of the untreated survivors. Sixteen patients were partially disabled and 12 totally disabled. There was no follow-up in five patients.

Of 69 patients surviving carotid ligation, 48 were in full work (70%) as were 26 of 38 who had had intracranial operations on the aneurysms (68%).

Results of Treatment According to Site of Aneurysm

Anterior Cerebral-anterior Communicating Aneurysms.—Table VI shows our results for aneurysms on the proximal part of the anterior cerebral artery or on the anterior communicating artery, the commonest site in our experience.

TABLE VI
ANTERIOR CEREBRAL—ANTERIOR COMMUNICATING ANEURYSMS

	Category A		Category B		Category C	
	No.	Deaths	No.	Deaths	No.	Deaths
Untreated	17	15	13	7	3	0
Removal of clot	4	3	—	—	—	—
Exploration only	—	—	2	2	—	—
Carotid ligation	1	1	—	—	—	—
Proximal clip	11	4	26	8	—	—
Clip to neck or excision	1	1	1	1	—	—
Totals	34	24	42	18	3	0

Untreated Patients.—The 17 untreated Category A patients behaved as follows: Five died before investigation, two following a negative angiogram, five had severe neurological disability, two were deteriorating, one died before a planned operation, one was considered too old for surgery, and the final patient did not tolerate carotid compression.

Of the 13 untreated Category B patients, two died from a further haemorrhage before a planned operation, six had an anomaly of the circle of Willis which it was believed would make a proximal clip a hazardous procedure, one did not tolerate carotid compression, one was thought to be too old for operation, and one was seen five weeks after the haemorrhage when she was well. One patient also suffered from haematuria for which reason he was transferred for investigation of the renal tract, and the final patient was rejected for surgery because there was some doubt about the presence of an aneurysm although a recent review of the angiograms confirmed that one was present.

The three Category C patients were untreated only because they had remained well following haemorrhage over eight weeks before admission to our unit.

Surgically Treated Patients.—Two Category B patients had died following a craniotomy at which it was found inadvisable to clip the anterior cerebral artery.

One Category A patient and two Category B patients had died from recurrent subarachnoid haemorrhage after operation to affix a proximal clip, although in one necropsy showed that the tantalum clip had not been completely closed over the artery. Four Category B but no Category A patients had had an intracerebral clot removed at the craniotomy and all had survived.

Late Results of Treatment.—Of the 11 untreated survivors, eight had returned to full work and two were totally disabled. There was no follow-up in the remaining case.

The one patient who had survived removal of an intracerebral clot remained totally disabled.

Sixteen survivors of a " proximal clip " operation were at full work, four were partially disabled, and five totally disabled.

Blood Pressure and Time of Operation Related to Survival.—The mortality of untreated normotensive patients was 61% and of hypertensives 74%. Of the surgical group the mortality of the normotensives was 24% and of the hypertensives 59%.

Twelve patients were operated upon within three days of haemorrhage with a mortality of 50%, nine between four and seven days with a mortality of 44%, eight in the second week of whom five died (62%), and 13 after two weeks with only two deaths (15%).

Disability Produced by Operation.—After an anterior cerebral clip had been affixed, four patients developed increased mental changes and three increased hemiplegia so that at the follow-up five patients may have had a disability which had been produced by the operation.

Internal Carotid-posterior Communicating Aneurysms.—In our series this was the second commonest site for ruptured aneurysm and Table VII shows our results for this group.

TABLE VII
INTERNAL CAROTID—POSTERIOR COMMUNICATING ANEURYSMS

	Category A		Category B		Category C	
	No.	Deaths	No.	Deaths	No.	Deaths
Untreated	5	5	3	1	1	0
Carotid ligation	7	4	36	6	2	0
Clip to neck and trapping	1	1	3	0	—	—
Totals ..	13	10	42	7	3	0

Untreated Patients.—Three Category A patients had not tolerated carotid compression, one died immediately after angiography, and the final one was thought to have had two aneurysms. One Category B patient had had no angiogram as she had not tolerated carotid compression and the other two were seen some weeks after subarachnoid haemorrhage at which time they were well.

Surgical Patients.—Our usual practice when surgery was decided upon was to ligate the common carotid artery in the neck and to evacuate an intracerebral haematoma when necessary. Two Category A patients only had an intracerebral clot evacuated, both of whom died. One Category A and 11 Category B patients developed a hemiplegia postoperatively and six of these died, two had permanent severe disability, and four recovered. Five hemiplegias occurred in the nine patients operated upon within 24 hours of haemorrhage, in three of the 10 operated upon between two and seven days, in one of the nine operated upon in the second week, and in three of the 15 operated upon after two weeks but none in those patients operated upon more than six weeks after haemorrhage.

The overall mortality for carotid ligation was 22%. Recurrence of haemorrhage after carotid ligation occurred with certainty in three hypertensive patients and possibly in two others as well.

Intracranial Operation.—The intracranial operations were clipping of the neck of the aneurysm in two patients and trapping in two others.

Relation of Blood Pressure and Time of Operation to Mortality.—The mortality of the untreated normotensive patients was 25% and of the hypertensives 100% (five cases) and for the treated normotensives it was 11% and for hypertensives 30%.

Five of 15 patients operated upon within three days of haemorrhage died (33%), three of the 17 operated upon from four to 14 days after the bleed (18%), and four of the 17 operated upon more than two weeks after the haemorrhage (23%).

Latest Follow-up Results.—The three untreated survivors were all at full work as were the three who survived an intracranial operation. Thirty-five patients survived a carotid ligation, of whom 28 were at full work, three were partially disabled, and one was totally disabled. There was no follow-up information in the other three patients. In only two instances could the disability at follow-up be attributed to the operation.

Middle Cerebral Aneurysms.—Thirty-nine patients had one middle cerebral aneurysm and Table VIII gives our results for this group.

TABLE VIII

RESULTS OF TREATMENT OF MIDDLE CEREBRAL ANEURYSMS

	Category A		Category B	
	No.	Deaths	No.	Deaths
Untreated	2	2	2	1
Removal of clot	2	2	—	—
Carotid ligation	7	5	16	2
Exploration only	—	—	1	1
Craniotomy	4	3	5	2
Totals	15	12	24	6

Untreated Patients.—Two died before angiography and one after a normal angiogram. The final patient was well when first seen one month after subarachnoid haemorrhage.

Treated Patients.—Angiography had not demonstrated the aneurysm in the two patients whose only treatment was removal of an intracerebral clot.

Carotid Ligation.—During the period under review we were treating middle cerebral aneurysms by common and then internal carotid ligation in the neck and evacuation of an intracerebral haematoma if necessary. Four Category A and two Category B patients had intracerebral clots removed and all six patients died. Six patients developed hemiplegia after carotid ligation, two of whom died, two recovered completely, and two partly. Subarachnoid haemorrhage recurred in three patients after common carotid ligation, and all died, and in one patient after common and internal ligation but he survived.

Craniotomy.—The procedures in these patients were excision in three and trapping in one, all of whom died, obliteration of the aneurysm by tantalum clips in one, and clipping of the neck of the aneurysm in four, one of whom died.

Blood Pressure and Time of Operation Related to Mortality.—In the untreated group one normotensive and one hypertensive patient died but the blood pressure was not recorded in the other two, of whom one survived. Fourteen normotensive patients had a carotid ligation and two died (14%), whereas of the nine hypertensives five died (55%).

For patients operated upon in the first three days the mortality was 58%, in the rest of the first week it was 33%, in the second week it was 36%, and after that 12%.

Late Results of Treatment.— The one untreated survivor had returned to full work. Three survivors of craniotomy were at full work and one was partially disabled. Of the 17 survivors of carotid ligation, 10 were at full work, four were partially disabled, and two were totally disabled.

Multiple Aneurysms.—Table IX shows our results in this group of patients with more than one aneurysm, but it must be appreciated that in any individual not all the aneurysms present were necessarily demonstrated by angiography.

TABLE IX
RESULTS OF TREATMENT OF MULTIPLE ANEURYSMS

	Category A		Category B		Category C	
	No.	Deaths	No.	Deaths	No.	Deaths
Untreated	11	9	14	3	1	0
Removal of clot	1	0	—	—	—	—
Carotid ligation	5	4	7	1	1	0
Intracranial operation	1	1	3	1	—	—
Totals ..	18	14	24	5	2	0

Untreated Patients.—Of the 11 Category A patients, two died before investigation, one before a planned operation, and the other eight were refused surgery solely because of the multiplicity of the lesions. It was for this reason that all Category B and C patients who were untreated were denied surgery.

Treated Patients.—Surgical treatment was instituted in patients with more than one aneurysm for one of four reasons: (1) Only one aneurysm was demonstrated by angiography. (2) Both aneurysms could be treated by the same operation, *e.g.*, carotid ligation, or through the same craniotomy approach. (3) There were conclusive signs indicating which aneurysm had ruptured. (4) An intracerebral clot was present and required evacuation.

In three instances the only aneurysm shown was treated, in three the supposedly ruptured aneurysm was operated upon, 10 were treated by carotid ligation, and in one patient two aneurysms on the same middle cerebral artery were clipped.

In only one patient did necropsy show that two aneurysms had ruptured but this patient had died before angiography.

Carotid Ligation.—Three Category A and one Category B patients had had an intracerebral clot removed in addition to ligation and two of these had died. Two Category A and two Category B patients developed a hemiplegia after ligation. The former two died and the latter pair made an almost complete recovery.

Intracranial Operations.—In three patients the ruptured aneurysm was clipped at its neck and one died, and the fourth patient had the aneurysm trapped but he also died.

Relation of Blood Pressure to Mortality.—Ten untreated patients were normotensive, of whom four died (40%), and 15 hypertensive, of whom seven died (47%). The mortality of the surgically treated normotensive patients was 31% and of the hypertensives 48%.

Latest Results of Treatment.—Ten untreated survivors were at full work, two were partially disabled, and two totally disabled. Nine surgical survivors were at full work, one was partially disabled, and one totally disabled.

Terminal Carotid Aneurysms.—Table X shows our results for aneurysm in this situation.

TABLE X
RESULTS OF TREATMENT OF TERMINAL CAROTID ANEURYSMS

	Category A		Category B	
	No.	Deaths	No.	Deaths
Untreated	—	—	2	2
Removal of clot	3	3	—	—
Carotid ligation	10	5	8	3
Muscle wrapping	1	0	—	—
Totals	14	8	10	5

Untreated Patients.—One died before angiography and the other had a normal angiogram.

Treated Patients.—No angiogram was performed on any of the patients whose only treatment was evacuation of an intracerebral clot.

Carotid Ligation.—Four Category A patients and one Category B patient had had an intracerebral clot removed in addition to the ligation and three of the former died. Two Category A and four Category B patients had had the internal carotid artery ligated two or three weeks after common carotid ligation without further mortality. Hemiplegia followed common carotid ligation in four patients, three of whom died but the fourth recovered so as to be able to carry on with her housewifely duties. Four patients had a recurrence of haemorrhage after carotid ligation but in three the necropsy showed an infarcted hemisphere also and this might well have been the cause of death.

Relation of Blood Pressure and Time of Operation to Mortality.—Eight normotensive patients had had a carotid ligation, of whom three died (37%), whereas five of 10 hypertensive patients succumbed (50%).

Seven of the 14 patients operated upon within a week of haemorrhage died (50%) and one of three operated upon in the second week.

Late Results of Treatment.—Of the patients who survived surgical treatment, six were at full work, two were partly disabled, and two totally disabled. There was no follow-up in one patient.

Distal Anterior Cerebral Aneurysm.—There were six patients with an aneurysm on the anterior cerebral artery distal to the anterior communicating artery. One patient died before investigation and one first seen five weeks after haemorrhage was also denied surgical treatment.

Treated Patients.—One patient had had an evacuation of an intracerebral haematoma before angiography but he died. Three patients had had a direct attack on the aneurysm which all survived.

Late Results.—The untreated survivor remained well as does one of the surgical patients but the other two were disabled, one partially and one totally.

Basilar Aneurysms.—Six patients had basilar aneurysms, three Category A, of whom one survived, and three Category B, all of whom died. One patient died before investigation and two after negative carotid angiography. The aneurysm was diagnosed by vertebral angiography in the other three patients. The only survivor was known to be alive two years later.

Posterior Cerebral Aneurysm.—There was only one such case and this was diagnosed by vertebral angiography in a patient who has remained well during follow up.

Posterior Inferior Cerebellar Artery Aneurysm.—Again we had only one example which was found at post-mortem examination, the patient having had a negative carotid angiogram shortly after admission.

Aneurysms at Other Sites.—Two patients had aneurysms on the peripheral branches of the middle cerebral artery; both were Category A patients who were treated by the removal of an intracerebral clot and neither patient survived operation.

One patient with normal carotid angiograms was found at necropsy to have an aneurysm in the wall of the lateral ventricle. Her only treatment had been evacuation of an intracerebral clot carried out under artificial respiration.

Patients not Referred to the Neurosurgical Unit

To get a true picture of the course of patients with subarachnoid haemorrhage we felt that it was essential to obtain information about all those patients admitted to associated hospitals but not referred to our unit. To obtain such information the physicians were asked to cooperate in completing questionnaires about the patients with proven subarachnoid haemorrhage admitted during the relevant period (April 1, 1954, to June 30, 1956) eliminating as far as possible those patients with a primary intracerebral haemorrhage. This was necessary for we wished to compare the fate of these patients with those reported by other authors where primary intracerebral haemorrhages were also excluded. In general, the older hypertensive patient who developed a severe hemiplegia as a result of a cerebral catastrophe was excluded unless the necropsy showed the presence of an aneurysm or an angioma. As very few necropsies were performed upon this group of patients the figures are not unduly weighted with those patients with aneurysms who had died and of course, some patients with primary intracerebral haemorrhage who survived without gross neurological defect might also be included. We realized the limitation of this form of review and its inaccuracies, but felt that it might be of some help in assessing the results of surgery in those patients with subarachnoid haemorrhage due to ruptured aneurysm.

Case records of 340 patients were considered suitable for inclusion, of whom 92 had been shown to have an aneurysm either by angiography or at necropsy. Ten had an angioma and 16 had negative angiograms. Twelve patients with aneurysms had been operated upon at other neurosurgical units. Analysis of this group of patients revealed that their average age was slightly higher than that of the patients admitted to the neurosurgical unit (56 years compared with 49 years), and that 59% were hypertensive compared with 48% of those admitted to our unit. This difference may have been only a reflection of the poorer prognosis in the older and hypertensive patient.

Of the 340 cases, 198 died (58%), 58 dying within 24 hours of the onset of haemorrhage. Five of the 12 patients treated at other neurosurgical units also died (42%).

The true picture of the mortality of patients with subarachnoid haemorrhage admitted to general hospitals associated with our unit can only be obtained by combining the two groups of patients, those transferred to a neurosurgical unit and those not so transferred. Thus we have a total of 748 patients (Table XI) of whom 337 died (45%), a

TABLE XI

RESULTS IN ALL CASES OF SUBARACHNOID HAEMORRHAGE

	Outside Hospitals		Neurosurgical Unit		Totals	
	No.	Deaths	No.	Deaths	No.	Deaths
Aneurysms	92	87	261	120	353	207
Angiomas	10	5	26	7	36	12
Other causes	—	—	3	0	3	0
Unexplained	238	106	118	12	356	118
Totals ..	340	198	408	139	—	—

Totals of all cases: 748—deaths 337 (45%)

mortality given by Walton (1956) as the average for conservatively treated series of patients reported in the literature, but usually calculated only from hospital deaths. Walton's figures for the same period of time (first eight weeks) was also 45% and in our series for the same period was 40% (296 deaths out of 740 patients).

Discussion

Our results for treatment of aneurysms both collectively and at the different anatomical sites show a lower mortality for surgically treated patients. Reasons can, however, be found to explain the poorer results of the untreated patients and to show that the operated patients are a somewhat selected group, albeit selected by the natural course of the disease rather than the deliberate selection of the surgeon. One large group of untreated patients is that with anterior communicating aneurysms, 33 patients with a mortality of 67%. We find, however, that some patients died before investigation and some after a negative angiogram so that these patients cannot be compared with any surgical group where demonstration of the aneurysm was an essential preliminary to surgery. In addition some patients died between angiography and the time for a planned operation and these again must be excluded for purposes of comparison. Excluding such patients we are left with only 15 untreated patients of whom six died (40%). In contrast 39 patients had an operation with the intention of clipping the anterior cerebral artery, although in two this was not in fact done, of whom 14 died (38%), whereas the mortality for all patients undergoing craniotomy was 39%. Our apparent surgical success may thus easily be explained away.

Of the nine untreated patients with internal carotid aneurysms, only three had had a positive angiogram and all three survived. Similarly of the untreated patients with a middle cerebral aneurysm, only one had a positive angiogram. These groups of untreated patients are too small for comparative purposes.

The group of patients with multiple aneurysms naturally includes patients whose only reason for being denied surgery was the presence of multiple aneurysms and the impossibility of determining which one had ruptured. These might form a suitable control group to compare with the treated patients. Twenty-three such patients were untreated with nine deaths (39%). After demonstration of the aneurysm by angiography, 17 patients were subjected to operation, of whom seven died (41%). Although it is agreed that there will again be differences between the untreated and treated groups as far as blood pressure, age at time of admission or operation are concerned, these differences will be of a more random nature than in the groups of patients with a single aneurysm previously discussed. In our group of patients with more than one aneurysm, therefore, we have shown that the untreated patients fare as well as the treated patients considering only those who have had aneurysms demonstrated by angiography.

Let us compare the results of the untreated and treated patients for the whole group of intracranial aneurysm discarding in the same way as above patients who cannot reasonably be included. We have now a group of 45 untreated patients, of whom 16 died (36%). (The patients with basilar and posterior cerebral aneurysms have been excluded.) One hundred and sixty-three patients were operated upon after an aneurysm had been demonstrated and of these 56 died (34%). Obviously there is no significant difference between the groups.

Considering Category A patients the mortality of the untreated patients (with the exceptions as before) was 72% and of the treated patients 64%. The difference is not statistically significant because of the small numbers involved—11 and 63 patients.

Category B patients who were untreated had a mortality of 28% (excluding patients with no angiogram or normal angiogram) whereas the surgical mortality of Category B patients was 25%. Again there is obviously no statistical difference.

This analysis shows that, for the period of time we have been able to follow these patients, the mortality of untreated patients and treated patients is the same if we make an endeavour to compare only those cases with similar features. In fact, more detailed analysis of the groups shows that the surgical group does contain the more favourable patients, *i.e.*, normotensive, younger age groups, Category B, operation after one week, etc., which but reveals the impossibility of a retrospective statistical analysis.

We next compared the results of treatment in all patients with subarachnoid haemorrhage admitted to our associated hospitals with groups of patients reported in the literature, the vast majority of whom had been treated conservatively. The average for reported series of patients is 45% (quoted by Walton, 1956), although, unfortunately, the range in the different papers is great. Walton's figures for his own large series is, however, in agreement with the average. We found that for 748 cases with subarachnoid haemorrhage admitted to hospitals with which we are associated, the mortality was 45% (follow-up time varying from a month to three years) but only 40% in the first eight weeks although over a quarter of these patients were operated upon. Certainly any surgical success we may have had does not appear to have significantly altered the

average outlook for the patients with subarachnoid haemorrhage admitted to general hospitals.

Any analysis of our figures which makes some attempt to obtain comparable untreated and treated patients fails to reveal any statistical difference in mortality, and, indeed, statistical evaluation is not usually necessary for it to be apparent that the untreated patients fare as well as the treated ones.

Conclusion

At the present time there is no conclusive evidence indicating the natural death rate in a large series of unselected cases of ruptured intracranial aneurysm and so there can be no proof of the value of surgical treatment in this condition. Manipulation of the figures for our own large series of patients can readily show that the untreated appear to fare as well as those operated upon. We have thus been forced to the conclusion that the truth of this controversial matter can only be established by a pre-planned campaign.

After consultation with neurologists in no way associated with our unit and with a statistician, we formulated such a scheme and put it into action on January 1, 1958. Briefly, all patients suffering from a ruptured aneurysm, which has been demonstrated by angiography and which, in the opinion of the surgeon, is amenable to surgical treatment, will be admitted to the trial series. Conservative or operative treatment will be allotted by random selection from previously prepared cards.

It will probably be necessary to acquire some 350 patients in the trial series in order to obtain a significant result which we hope to achieve in a period of less than two years. It will then be possible, for the first time, to determine the natural death rate of the condition and the results of surgical treatment at our hands.

We wish to thank Mr. Valentine Logue for permission to use records of patients who were under his care and also the many physicians of associated hospitals who so readily made available details of their patients with subarachnoid haemorrhage.

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LEUCOTOMY FOR PAIN

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Leucotomy is advised for a patient whose main complaint is pain generally as a last resort and not because careful consideration shows that this is the treatment of choice. There is general agreement that the operation should not be performed if there are grounds for thinking that some other treatment will provide effective relief, but many clinicians only advise leucotomy when all other possible procedures have been tried and have failed. McKissock (1953) has stigmatized this as bad practice and few will disagree with his view that what in a final analysis proves the most beneficial operation should be the initial one. This can only be so if it is possible to select those patients with complaints of severe pain, for whom leucotomy is the best treatment, balancing probability of benefit against risk of harm.

The patient who suffers from pain for any considerable length of time has to contend not only with the pain itself, but also with a variety of psychological effects secondary to the pain such as anxiety, introspection, distressful rumination, and depression. His disability is complex, and this may explain why the views of different authorities vary so widely as to the significance of these psychiatric factors. Thus Freeman and Watts (1950) say that " generalized pain and distress can be alleviated more readily than pain and distress due to direct involvement of nerve trunks ". This view is also supported, amongst others, by Grantham (1950), Smolik (1950), and one of the major French schools (Petit-Dutaillis, Messimy, and Berges, 1953). In sharp opposition, other authorities report that better results are obtained where the psychological reaction is minimal (Scarff, 1950; King, Clausen, and Scarff, 1950). Dynes and Poppen (1949) also claim that patients with metastatic malignant disease with good pre-operative personalities responded best. Similarly Le Beau and Gaches (1949) found their best results in patients with an organic basis for their pain and no abnormal mental state. Le Beau has modified this opinion; he elaborates a concept of "*souffrance*", a state of painful mental anguish, which he regards as the main indication for psychosurgery (Le Beau, Choppy, Gaches, and Rosier, 1954).

These different views may not reflect incompatible observations. What is generally missing is an analysis in formal psychiatric terms of the character of the complaint of pain, and the relation of this analysis to the final outcome. Thus there is general agreement that while leucotomy does not alter the patient's ability to perceive pain it does alter the psychological components of the pain situation. A logical consequence of such a premise is that the aim of the operation is to produce a change in personality. It is generally hoped that this change will be solely beneficial, in that the patient will become less sensitive to his pain without being any less sensitive to his social environment. Indeed many authorities appear to believe that leucotomy can produce relief of intractable organic pain without significant personality deterioration. This belief is usually based on experience with a modified operation. There are, it is true, several reports of the successful use of standard bilateral leucotomy for pain without loss of social adjustment, but it seems clear that in every case the adjustment has been in the face of personality deficits of the frontal lobe type.

Modified Operations

There are three ways in which a modified operation on the frontal lobes might relieve pain.

In the first place, there might be a selective interference with the perception of " autonomic " or visceral pain. Workers at Yale (Hamlin, Delgado, Chapman, and Rosvold, 1953) have claimed that it is possible to relieve intractable visceral pain by producing small focal electrolytic lesions in the ventromedial part of the frontal lobes. However, it has never been shown that after orbital damage there is abolition or reduction of the perception of experimentally induced visceral pain.

Secondly, a small focal lesion might cause a specific inattention or dysgnosia for the painful aspects of a stimulus, which would, nevertheless, be perceived. This phenomenon, often described clinically, has been called asymbolia for pain (Schilder and Stengel, 1931).

The third way in which a modified operation might help would be by causing a generalized impairment of the ability to form appropriate emotional responses. In such a case the desired lack of distress on receipt of the distressing painful stimulus would be but a part of a wide range of incapacities which could be classified as deterioration of personality. Cobb and his colleagues at Harvard (Bonner, Cobb, Sweet, and White, 1953) studied a series of 38 patients who had undergone a variety of operations: bilateral standard leucotomy, bilateral lower quadrant frontal leucotomy, unilateral frontal leucotomy on the dominant side and unilateral excision of the orbital cortex. Their results indicated that the degree to which pain is relieved is closely paralleled by the extent of deterioration of personality, and they concluded that such operations could be justified " only in very special circumstances ". There are many other authorities, *e.g.*, Petit-Dutaillis *et al.*, (1953) who believe that some impairment of personality is a price that has to be paid before an operation on the frontal lobes will relieve pain or the distress it causes.

Material and Methods

The present study is based on the results obtained with 25 patients who underwent leucotomy-type operations for the relief of intractable pain. These patients form part of a larger series treated by leucotomy. Many others in this series complained of various pains, but in the 25 cases reported here pain was the initial complaint and the patient was referred for consideration of leucotomy in the belief that it was pain which determined his disability. All patients had previously been extensively investigated medically and neurologically and in nearly all cases an adequate presumptive physical cause for the complaint of pain had been demonstrated. No attempts were made to reproduce patients' pain experimentally. A separate study on the effect of leucotomy on the individual's tolerance and reactivity to pain has already been reported (Elithorn, Piercy, and Crosskey, 1955).

The clinical difficulty of assessing the severity and intractability of a physically painful lesion has recently been discussed by Botterell, Callaghan, and Jousse, (1954) and by Turnbull (1954). The latter has pointed out that not only was there a small proportion of terminal cases of carcinoma of the cervix in which intractable pain was not reported, but also that the estimations of gynaecologists as to the incidence of intractable pain amongst their cases varied widely—from negligible to 100%. The presence, therefore, of an organic lesion, known to be severely painful in some patients, does not prove that in any given case the patient suffers severe pain due to organic nerve involvement.

In the present instance an estimate of the physical importance of the " organic " element in the pain situation was derived partly from the consistency and verisimilitude of the patient's account of his pain, partly from the signs of distress observed when the patient was not aware that he was under surveillance, and partly from the relatives' story as to the amount the pain interfered with the patient's activities when he was not—as he was in consultation—directing his whole attention to a careful appreciation of his symptoms. A history of previous breakdowns in relation to psychological stresses was also admitted as evidence; the more easily the patient had become distressed in the past, the less severe would be the pain which one would assume to cause any particular degree of present disturbance. This estimate of the severity of the organic pain for the present 25 patients is given in Table I.

With four patients (classified ++++) there could be little doubt that the disabilities were severe and very painful. In nine other cases (+++) marked organic pain was the central feature and presumptive cause of the illness. In seven cases (++) organically determined pain had precipitated or determined a psychological reaction which was the major disability. In five cases (+) the complaint of pain, even though based on organic pathology, was thought to be chiefly determined by the psychiatric condition.

After in-patient observation the available evidence was discussed at a conference attended by all members of the department. The operation was then recommended to the patient and relative in terms of the probability of worth-while relief. The final decision was left to the patient.

After the operation and a period of in-patient rehabilitation, the patient and his relatives were required to attend a special follow-up clinic. At this clinic a consistent drive was made to help the patient over every hurdle facing him, to get him to take up as normal a way of life as possible, and to get him back to work.

For the purpose of the present investigation each patient attended for a formal assessment. This interview took place on an average 23·6 months (range six to 58) after the operation. Most patients have been seen frequently since their attendance for this assessment, and the overall evaluations of the operations are derived from all the information available. The minimum follow-up period is thus 17 months, the longest 78 months, with an average of 40·3. The duration of the follow-up in individual cases is given in Table I.

At the formal assessment the patient was asked the following questions: Had the operation helped him; if so, which symptoms had improved? If not, had any symptoms improved ? Which symptoms had not improved ? Had any bad effects been noticed ? Had there been any change in his personality ? What was his own rating of the operation, was he glad he had had it, did he regret it, or was he unable to say ? A very similar list of questions was put to the relative, who was furthermore asked about social effects. Both patient and relative were then taken through a list of the complaints suffered before operation, and asked what change there had been in respect of each of them.

Whoever makes it, the evaluation of leucotomy as a treatment is in the final analysis a subjective one. The importance of giving due weight to the views of the patient and the relatives has recently been emphasized elsewhere (Elithorn and Slater, 1956). In the present series the

authors agreed together that more than two-thirds of the patients had benefited from leucotomy. In sharp contrast two-thirds of the patients and relatives felt that the operation had not helped. This conflict of opinion appeared to reflect the fact that the patients and their relatives were concerned primarily about the failure of the operation to relieve the pain whereas the authors were more influenced by an overall appraisal which included such variables as an improvement in mood, a better social adjustment, and an apparent reduction in suffering.

In an attempt, therefore, to provide a more objective picture of the effect of the operation on the patient's behaviour a social behaviour rating scale was devised. Such a rating scale still depends on the subjective evaluation of quantitative data but does, nevertheless, permit a more detailed assessment of the efficacy of treatment. The patient's social behaviour was related to this scale for each year of his illness and of the post-operative follow-up period. The scales were as below:

Results

It should perhaps be emphasized that the results reported and discussed here are those found at follow-up not less than six months after the operation. Immediately after the operation, many patients showed much greater improvement than that now

I. SYMPTOMS

Score	Criteria
	A. Patient's reaction
5	Symptom free; in excellent form
4	Occasionally mild symptoms—never complains spontaneously; no specific symptoms but not really well
3	Occasional moderate or persistent slight symptoms; complains rarely or only when asked
2	Severe symptoms occasionally; moderate persistent symptoms, complains sometimes
1	Persistent, severe symptoms which can be borne; occasional times of relative ease; complains frequently
0	Constantly complaining; state unendurable; suicidal risk
	B. Social reaction
5	No demands to be met by family or hospitals
4	Family life largely unhindered by patient's symptoms
3	Patient's symptoms occasionally disrupt family life; occasional treatment provided
2	Symptoms and general condition often have to be considered and allowances made by rest of family or friends; routine treatment required
1	Family, friends, or hospitals receive frequent and heavy demands; regular treatment necessary
0	Family life revolves around patient's illness; constant attention, sympathy, or treatment given

II. EMPLOYMENT

Score	Criteria
	A. Amount
5	Full-time employment with changes only for the better; independent; provides for others
4	Full-time employment with short periods off work; three-quarter time steady; occasional changes in same type of job; independent with some difficulty
3	Half-time regular employment; full-time with frequent changes in same status job; largely independent; some help needed to meet commitments
2	Half-time work; regular periods off; frequent changes to poorer jobs; needing much economic help
1	Odd jobs of casual work; mainly dependent upon State, social agencies, or relatives
0	Given up working altogether; parasitical
	B. Performance
5	Proficient; responsible; reliable; enterprising
4	Generally efficient and adequate; occasional help or support needed; tidy; clean; uses thought and plans work
3	Adequate and neat, but support and allowances needed; routine work requiring no responsibility
2	Poor, untidy, careless or erratic; supervision needed, but can be relied upon to carry out instructions
1	Passenger; neglectful and dirty; retained out of sympathy; constant support or supervision needed
0	Liability; a responsibility or hindrance to others

III. FAMILY RELATIONSHIPS

Score	Criteria
	A. Responsibility
5	Takes a fully responsible role; takes other members' wishes into account; budgets and manages affairs well
4	Responsible and manages well; some help and direction from others needed; living within income
3	Accepts routine or habitual spheres of responsibility; takes a responsible role only when pushed; living at income level
2	Displays very limited or habitual responsibility with encouragement; occasional display of responsibility when absolutely necessary; lacking forethought; living slightly beyond means
1	Completely dependent; no concept of value of money
0	Only self-concerned; scrounges
	B. Affect
5	Spontaneous feeling and concern for others; warmth of personality ; dependable
4	Predominantly affable and dependable; spontaneously friendly; occasionally helpful
3	Considerate and cooperative only when necessary; responsive to affection though lacking in initiative
2	Largely indifferent; sometimes querulous but amenable
1	Contentious; self-concerned
0	Negativistic; hostile; demanding of much attention

IV. COMMUNITY RELATIONSHIPS

Score	Criteria
	A. Social graces
5	Charming, pleasant, easily makes spontaneous personal relationships; tactful; a good sense of interdependence
4	Friendly; affable; able to accommodate to others with ease; a good sense of appropriate social behaviour
3	Cooperative and friendly only occasionally; polite, responds to rather than initiates social intercourse
2	Some difficulty in forming social relationships but desires them; can be pleasant at times but rather lacking in tact
1	Reluctant to engage in social intercourse; domineering or imperious; ungracious; completely lacking in thought for others; apathetic
0	Social manners repugnant or offensive to others; constantly arousing displeasure
	B. Leisure activities
5	Spontaneous social or cultural interests; participates with initiative; a good sense of social obligation; balanced and versatile in approach to leisure activities
4	Interest and activity with some initiative; but often passive; having some creative or cultural hobbies or a single enthusiastic activity
3	Spasmodic or transient active interests; completely passive but steady interests; sense of social responsibility only with support
2	A very limited sphere of interests; only passive hobbies, *e.g.*, cinema; a tendency to be concerned only with personal rights rather than social obligations
1	Asocial; no interests; tendency to lead the life of a social hermit
0	Anti-social trends

TABLE I

BASIC DATA

Case No.	Sex Age	Diagnosis	Main Psychiatric Reaction	Degree of Pain	Duration of Pain (years)	Type of Operation
Extensive operation						
10	M 44	Postencephalitic torsion spasm; pain from involuntary movements	Depression, hysteria, paranoid	++++	3½	Standard
21	M 39	Torsion spasm; idiopathic, progressive; severe pain from movements	Depression, anxiety	++++	24	(i) Blind rostral (ii) Standard
24	F 45	Disseminated sclerosis; pain in left face persisting after fifth root section	Depression, anxiety, obsessional	++++	10	(i) Right unilateral (ii) Left lower quadrant
2	M 56	Postherpetic neuralgia ophthalmic division of trigeminal nerve; pain in left face	Depression, anxiety, obsessional	+++	2	(i) Open rostral (ii) Standard
3	M 72	Left hemiplegia; subsequent persistent pain of left arm of central origin	Depression	+++	5	Standard
5	M 78	Postherpetic neuralgia left scapular region, thoracic dermatomes 5-7	Depression	+++	2	(i) Blind rostral (ii) Right unilateral
17	M 52	Pharyngeal carcinoma; pain in face, discomfort from naso-pharyngeal fistula	Depression, anxiety, obsessional, hysteria, paranoid	+++	1½	Standard
9	M 50	Right pneumonectomy and thoracoplasty; persistent pain in right chest	Depression, anxiety, obsessional, hysteria	++	1	Standard
11	F 60	Trigeminal neuralgia; pain persisting in left face after fifth root section	Depression, anxiety, hysteria	++	5	Standard
Unilateral operation						
19	F 53	Postherpetic neuralgia; right dermatomes 5-6	Depression, anxiety, obsessional, hysteria	+++	2	Right unilateral
23	F 64	Postherpetic neuralgia; left dermatomes 7-11 persisting after rhizotomy	Depression, anxiety	+++	1½	Left unilateral
15	F 63	Trigeminal neuralgia; pain persisting in right face after 3 Gasserian ganglion injections	Depression, obsessional	++	11	(i) Right unilateral (ii) Fifth root section
Limited operation						
18	M 61	Spasmodic torticollis; gross arthritis of cervical spine; bilateral pain in neck and head	Depression, anxiety	++++	7	Lower quadrants
4	F 53	Cerebro-cerebellar degeneration; pain of thalamic type in right face	Depression, anxiety, obsessional, hysteria	+++	5	Blind rostral
14	F 70	Mycosis fungoides; painful irritation of skin	Depression	+++	6	Lower quadrants
22	F 50	Frequent migraine; eventually persistent pain in head	Depression, anxiety, obsessional, hysteria	+++	38	Bimedial (temporal)
1	M 56	Postherpetic neuralgia; left dermatomes 6-9	Depression, anxiety	++	1½	Blind rostral
12	F 68	Trigeminal neuralgia; pain persisting in right face after Gasserian ganglion injection	Depression, anxiety paranoid	++	10	Open rostral
20	F 39	Pulmonary tuberculosis, thoracoplasty; pain in chest and epigastrium	Hysteria	++	14	Lower quadrants
25*	M 42	Chronic gastric ulcer (undiagnosed); pain in abdomen and chest	Depression, anxiety, obsessional, paranoid	++	9	(i) Blind rostral (ii) Gastrectomy
6	M 42	Left cortical atrophy; persistent pains right side of head	Depression, hysteria	+	6	Cingulectomy
7	F 51	Subacute combined degeneration of cord; pains and paraesthesiae in legs, trunk, and arms	Depression, hysteria, paranoid	+	4	Bimedial rostral
8	F 31	Constant headaches since childhood; no cause found	Anxiety, hysteria	+	20	Bimedial rostral
13	M 58	Osteo-arthritis of spine; persistent pain in legs and abdomen	Depression, hysteria, paranoid	+	3½	Bimedial rostral
16	M 54	Cerebral arteriosclerosis; persistent pain in lower jaw following dental extractions	Anxiety, hysteria	+	15	Blind rostral

* This patient's pain, which persisted after leucotomy, was subsequently relieved by gastrectomy. Earlier and repeated investigations had fail

TABLE I—*continued*

BASIC DATA

ation of low-up onths)	Effect on Pain	Psychiatric Reaction Improved	Has Operation Helped ?				Regain on Final Follow-up Social Ratings (%)
			Patient	Relative	Physician	Extent of Personality Change	
2	No change	Depression	No	No	Improved	Marked	+ 7
0 (Died)	No change	Depression	—	—	Unimproved	Severe	− 17
8	Less severe	Less distressed	Yes	No	Worse	Marked	− 16
9	No change	Depression, anxiety, obsessional	No	Yes	Much improved	Definite	+ 50
0	Little change	Depression	No	Yes	Much improved	Marked	+ 59
0	No change	Depression	No	No	Much improved	Marked	+ 51
2 (Died)	No change	Depression, anxiety, hysteria	No	Yes	Improved	Definite	− 8
3	Worse	Depression	Yes	Yes	Improved	Definite	+ 37
8	No change	Depression	Yes	Yes	Improved	Severe	+ 69
4	No change	Depression	No	No	Unimproved	Slight	+ 33
7 (Died)	Worse	Less distressed	—	—	Worse	Definite	+ 28
0	No change	Anxiety, obsessions	Yes	Yes	Improved	Negligible	+ 42
6	Worse	Depression	No	No	Unimproved	Definite	+ 17
3 (Died)	No change	Depression	Yes	—	Much improved	Negligible	+ 23
4	Less severe	Depression	No	—	Improved	Severe	+ 14
2	Worse	Less distressed	No	No	Worse	Slight	− 36
5	Much better	Depression, anxiety	Yes	Yes	Much improved	Definite	+ 88
6	Improved	Depression, anxiety	Yes	No	Improved	Severe	+ 26
1	Much worse	Depression	No	No	Unimproved	Slight	+ 56
0	No change	Anxiety, obsessions	—	No	Worse	Definite	+ 27
3 (Died)	Much better	Depression	Yes	Yes	Much improved	Slight	+ 88
8	Worse	Depression	No	No	Improved	Definite	+ 55
3	No change	Depression, anxiety	No	No	Improved	Slight	+ 147
4	No change	Depression	No	No	Improved	Slight	+ 70
4 (Died)	No change	Depression anxiety	No	No	Improved	Definite	− 15

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TABLE II
MEAN SOCIAL RATINGS FOR WHOLE GROUP

Rating Scales (0—10)	(*a*) Premorbid	(*b*) Pre-operative	(*c*) Final Follow-up	$\frac{c-b}{a-b} \times 100$ Regain of Ground Lost
Symptoms (10 = symptom-free)	8·6	0·9	4·3	45%
Employment	8·5	1·6	3·4	27%
Family relationships	7·6	1·9	3·6	29%
Community relationships	5·7	1·8	3·4	40%
Mean values (for all four scales)	7·6	1·6	3·7	35%

recorded. Some reported total relief from pain. In the majority of cases, however, this returned within three months and by then became as bad as ever.

Table I presents the basic data for each patient. The results obtained with the rating scales are presented in Table II and discussed first. These are then related to the clinical assessments and the views of the patients and their relatives.

Fig. 1 shows an example of a rating profile. Such profiles were constructed for all 25 patients. For discussion here we have taken three corresponding points in each patient's history: The premorbid ratings, the immediately pre-operative ratings, and the final follow-up ratings. The mean values for these points are given in Table II. On the symptom scale the mean premorbid rating is 8·6, with 12 patients being symptom-free and scoring 10; none scoring less than 6. Pre-operatively the mean score falls to 0·9; at this level there is not only complete incapacity but life itself is almost unendurable. Only one patient scores as high as 3 and 11 score 0. The mean score at the final follow-up is 4·3, indicating the persistence of a moderately severe degree of suffering. Seven patients gain 1 point or less; none gain more than 7. The mean gain of 3·4 points following the operation, however, represents the regain of 45% of the ground lost from the premorbid

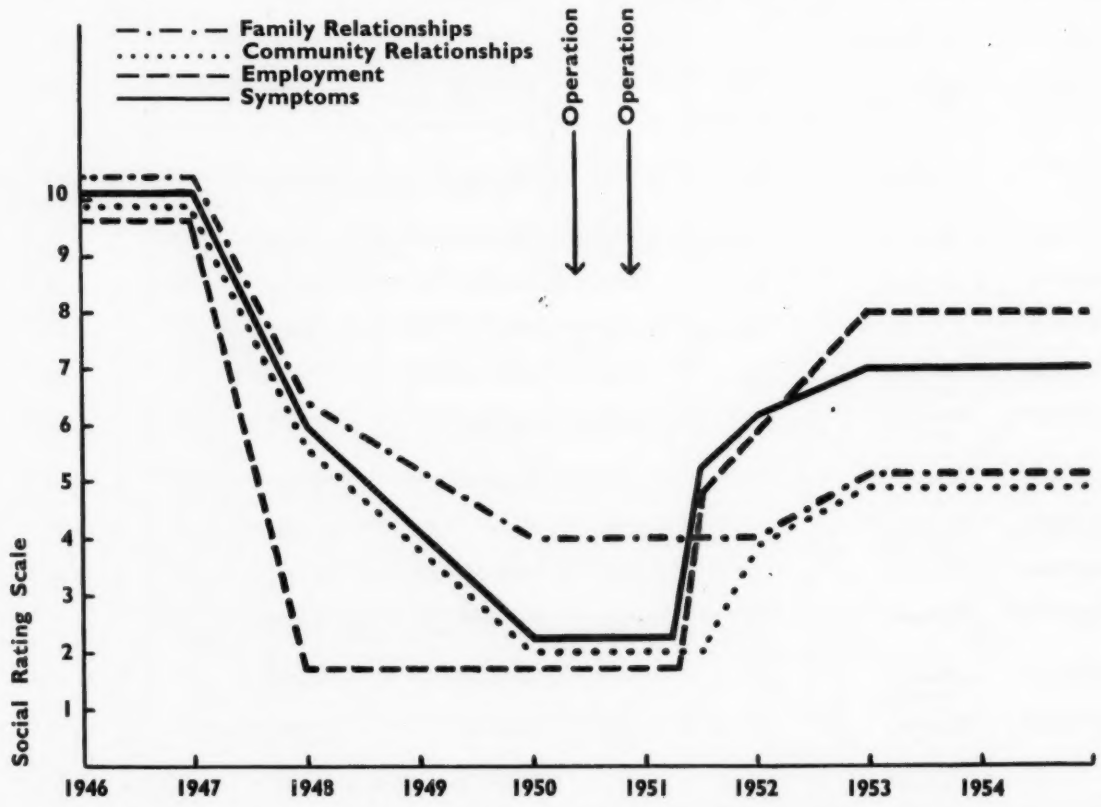

FIG. 1.—Social assessment rating profile (Case 2).

mean of 8·6. This degree of recovery is greater than that found in the other ratings.

The employment ratings show a similar picture. The premorbid ratings have a mean of 8·5. Before their illness 13 patients were in full effective employment and have ratings of 10, and only three have ratings below 7. Pre-operatively the mean rating has fallen to 1·6, the majority of patients showing almost complete dependence in the home and out of it. Eleven patients score 0, but it is noteworthy that even at this nadir in their lives three patients score 6 or 7. These exceptional individuals, all women, continued to work effectively in their homes in spite of frequent and bitter complaints of severe pain. At the final follow-up the mean rating has risen to 3·4, representing a very marked degree of persisting disablement, and a regain of only 27% of the ground lost through illness. However, great variability is shown. Eight patients score 0, three of them having dropped to this point from a slightly higher pre-operative level. On the other hand, seven patients have final scores of 7, 8, or 9, indicating a very satisfactory restitution of working powers. If, however, we look at the results obtained with three women who retained their capacity to work during their illness, we find that one had no relief of symptoms and still maintained her working capacity; another, with slight relief of symptoms, was almost back to full working capacity, while the third, with moderate symptomatic relief, became almost incapable of any work. The general correlation, in fact, is subject to noteworthy exceptions.

In the field of family relationships, we find a mean premorbid score of 7·6, seven patients scoring 10, and five scoring 5 points or less. Pre-operatively the mean score drops to 1·9, with eight zero scores and only two patients scoring as high as 6. At final follow-up the mean score has risen to 3·6, a regain of 29% of the ground lost by illness. The final score can hardly, however, be regarded as satisfactory.

In the field of community relations the ratings give, perhaps, a rather less depressing picture. The premorbid score is not high at 5·7, and one cannot say that our patients were as a group a very sociable lot of people. Premorbidly, the mean score falls to 1·8, rising again in final follow-up to 3·4, a regain of 40% of the ground lost.

Correlation coefficients which express the relationships between the changes in the different fields can be calculated. In the first place we may correlate the changes in scores which occur in the different fields between the pre-operative and follow-up ratings. These correlations are given in Table III. They are fairly high, and show that on the whole improvement or its reverse in any one field tends to go with similar changes in the other fields.

TABLE III

INTERCORRELATIONS BETWEEN FINAL FOLLOW-UP RATINGS

Rating Scale	S	E	FR	CR
Symptoms (S)				
Employment (E)	+ 0·55			
Family relationships (FR)	+ 0·60	+ 0·82		
Community relationships (CR)	+ 0·63	+ 0·68	+ 0·84	

As these four types of rating are closely correlated and have much in common, it is justifiable to sum them to obtain a more widely based estimate of psychological normality and successful social adaptation. If this is done for each patient at each stage, *i.e.*, premorbidly, pre-operatively, and finally, we may determine whether there is any correlation between the patient's ratings at each of these three times. If the three times of rating are numbered 1 to 3, then we have: $r_{1,2} = + 0{\cdot}26$, $r_{2,3} = + 0{\cdot}34$, $r_{1,3} = + 0{\cdot}27$. These positive correlations indicate that there is a " personal equation " affecting the degree of adjustment at each of the three stages, independently of the illness or its treatment, but that this not of a high order. This is what one would expect in the case of severe organic disorders subjected to an organic method of treatment.

Clinical Assessments

It is of interest to compare the assessments based on these ratings made independently by the psychiatric social worker and the holistic and impressionist views formed by the patient and the relative and in the clinic.

Twenty-three of the 25 patients survived to be asked six months or more after operation whether the leucotomy had helped them or not; 14 denied relief, one replied " yes and no ", and only eight (35%) answered affirmatively. Similarly of the 21 relatives who were asked whether the operation had helped the patient, only eight (38%) thought that it had. In only five cases (24%) did both patient and relative think the operation had helped. These replies compare very unfavourably with those obtained with other patients, leucotomized not for the relief of pain but for the treatment of primarily psychiatric illnesses. In this latter series 75% of 80 patients and 89% of 72 relatives thought that the operation had been of value to the patient.

Clinical assessment, based on interviews in the clinic and reports of behaviour at home and at work, indicated that the operation had been well worth while in over two-thirds of the cases: six were classified as " much improved ", 11 as " improved ", four as " unchanged ", and four were regarded as being " worse ". This discrepancy of views requires discussion. The social ratings strongly support the

TABLE IV
MEAN SOCIAL RATINGS FOR OPERATIVE GROUPS

	Premorbid				Pre-operative				Final Follow-up			
	E	S	FR	CR	E	S	FR	CR	E	S	FR	CR
Extensive operation	8·8	9·0	8·1	6·8	1·4	0·6	2·2	1·6	2·9	3·9	2·6	2·8
Limited operation	8·1	8·2	6·9	5·1	1·2	0·8	1·2	1·7	3·4	4·5	3·8	3·8
Unilateral operation	9·3	8·7	8·7	5·3	3·7	2·3	3·7	2·7	5·3	4·7	5·0	3·0

clinical assessment. If the total scores are considered 20 of the 25 patients (80%) showed some increase in score, though in six cases this was five points or less.

Experimental work (Chapman, Rose, and Solomon, 1950; Elithorn *et al.*, 1955) has shown that the perception of pain and the immediate responses to a painful stimulus are generally not reduced by leucotomy. It is therefore not surprising that patients whose main subjective complaint is unaffected by the operation should not regard it as a success. Of the 25 patients, 19 described their pains as unchanged or worse, only two described them as much better. Nearly the whole of the improvement observed clinically, therefore, was in the affective field, and this was reflected in an improved social adjustment. When faced with the observation that they were more effective people, the majority of patients did not deny this but claimed it was due to the successful outcome of their own determined struggle with a disability that had been essentially unaltered by leucotomy.

The Extent and Site of Operative Interference

Details of the various operative techniques employed are given in Table I. The techniques of the modified operations have been described elsewhere by the surgeons concerned (McKissock, 1953; Jackson, 1954). For the present analysis the operations have been divided into two classes: "limited" and "extensive". In the former the intention was to divide half or less of the white matter of the frontal lobes, in the latter more widespread damage was attempted: of these seven were full bilateral "standard" operations, two full unilateral operations with partial incisions on the contralateral side. Table IV shows the relationship between the extent of operation and the mean improvements on the pre-operative ratings. It must be remembered in comparing the results obtained with the two types of operation that such a comparison will show a bias against the extensive group, since this contains a few patients who first had a minor unsuccessful leucotomy and were subsequently operated on again. In the following analysis nine patients who had an "extensive" operation are compared with 13 who had a "limited" one. The three patients who had only a unilateral standard leucotomy have been omitted. In the extensive group three patients thought they had been helped, five thought not; in the second group the numbers are four against eight. In the first group the relatives thought the patient had been helped in five cases, not helped in three; in the second group the numbers are two and nine. Patients leucotomized for pain, therefore, show a very slight preference for an extensive operation. The relatives have a more marked and similar preference. The clinical assessment also attributes better results to the extensive operation: three out of nine are much improved in this group, and in the limited group only three out of 13 are so classified. Similarly, in the extensive group, two of the nine patients are classified as unimproved or worse, while in the limited group four out of 13 are so classified. These findings, though only suggestive, reflect the views of the patients and relatives in the larger series (Elithorn and Slater, 1956). Their main interest lies in the fact that they stand in sharp contrast to the observations made with the rating scales. Thus in the limited group there are four patients with 20 points of improvement or better; there are none in the extensive group. In the latter there are three patients who have minus scores, as against only two in the limited group. The mean improvement in the extensive group is 6·6 points, in the limited group 10·5 points. If we break down the limited group into small sub-groups, we find that the single patient submitted to cingulectomy gains 22 points. The four patients with bimedial opera-

GAIN ON FINAL FOLLOW-UP RATINGS FROM PRE-OPERATIVE RATINGS

	E	S	FR	CR
Extensive operation	+ 1·5	+ 3·3	+ 0·4	+ 1·2
Limited operation	+ 2·2	+ 3·7	+ 2·6	+ 2·1
Unilateral operation	+ 1·6	+ 2·4	+ 1·3	+ 0·3

E = Employment
S = Symptoms
FR = Family relationships
CR = Community relationships

tions average 11·5 points, the three patients with lower quadrant cuts average 9·7 points, and the five patients with rostral operations average 8·0 points.

This clear tendency for gains on the rating scales to be greater with the limited operations contrasts with the preference for the results obtained with the extensive operations shown by patient, relative, and clinician. They are all impressed in the first place by actual relief from suffering. Here extensive operations have a clear advantage and our observations support the findings of others who have emphasized that it is the quantity of frontal lobe damage which chiefly determines the degree of apathy towards pain. In the social assessment, more weight is given to differences in behaviour. The lives of many patients have improved, sometimes to a remarkable extent, yet the patients themselves and their relatives still believe that they have not been helped. In addition the social ratings place greater emphasis on the social effects of post-operative defects. Table IV shows the average number of points gained on each rating scale for the two groups.

Severity of the Painful Lesion

Careful study of these 25 cases shows that the more clearly it was established that the pain itself was severe the less effective was leucotomy as a treatment. Three of the four patients in the group with very severe pain (++++) were classified clinically as unimproved or worse after the operation, and the mean improvement on the social score is 0·0. In the next group (+++), three of the nine patients are unimproved or worse, and their mean improvement score is 6·8. In the next group (++) of seven, one is not improved, and one is worse; the mean improvement is 11·7 points. In the last group (+), in which the psychiatric element was thought to predominate, all improved clinically; the mean improvement is 14·0. This strongly supports the findings of those who believe that prefrontal leucotomy, even in an extensive form, is not an adequate method of treatment of severe organic pain.

Effect of the Psychiatric Concomitants

The work of Sargant, Partridge and Pippard, amongst many others, has established that in psychiatric cases some " psychopathological " processes respond better to leucotomy than do others. When the primary illness is an anxiety state, an obsessional disorder, or a non-cyclical depression, then the outlook with psychosurgery is far better than when it is schizophrenia, cyclical insanity, or a hysterical illness (Partridge, 1950; Sargant, 1953; Pippard, 1955, 1956). Preliminary analysis of the relationship between the degree of improvement and the psychological reaction shown by the present cases suggests that these findings do not necessarily apply to patients with intractable pain (see Table I). Thus it is not obvious that those in whom the psychiatric reaction was one of depression or anxiety have done better than those in whom the predominant attitude was thought to be an hysterical one. This difference in the present series reflects in part the overriding importance of the severity of the pain as the chief variable determining the outcome of any given operation. However, closer inspection of the material reveals that in these cases psychological mechanisms are affected in the same way as in purely psychiatric cases.

In 22 of the 25 cases depression was present. In 12 of them it was a marked symptom and in all but one (Case 7) it was reactive in type. Twenty patients with depression survived to be questioned; all but three reported some relief from this particular symptom. Four said that they were never depressed. However, this total abolition of depressive feelings was not confirmed by their relatives, who reported that although the symptoms of depression were less severe they did still occur. Characteristically, for all the patients there was a reduction in the duration of the periods of depression and frequently a decrease in the depth of the emotion experienced. Two patients, who before the operation had been consistently depressed, reported that subsequently this symptom was directly associated with attacks of pain (Cases 10 and 22). Clearly in these patients suffering pain, as in psychiatric patients generally, frontal lobe damage had greatly reduced the individual's ability to develop a depressive reaction. When such a reaction did develop it was relatively ill-sustained.

In 16 patients a tendency to anxiety was present. In all 16 cases operation produced a reduction in this tendency. In the case of the standard leucotomies this was often profound. The effect of this reduction on the total picture was, however, marked only in those four cases in which the anxiety was considered pre-operatively to have been excessive and of aetiological significance (Cases 1, 8, 12, and 25). Three of these four patients thought that the operation had helped them. The fourth, who showed marked hysterical features, not only said that the operation had not helped and that the pains were the same, but she also denied any reduction in her tendency to get tense and anxious. She did, however, admit to a decreased frequency of palpitations and to being much less worried by her specific fears of insanity and pregnancy. In fact, she was considerably better (Case 8).

In six of the present cases the disability was

thought to depend largely on hysterical mechanisms (Cases 6, 8, 9, 13, 16, and 20); in seven other cases hysterical mechanisms were thought to play a secondary role in determining the character of the illness. In these 13 cases the results were classified as improved in 10 and as unimproved or worse in three. Of the 12 patients in whom hysterical mechanisms were absent or unimportant, five were unimproved or worse and only seven improved. This finding is at variance with the observation that hysterical illnesses respond poorly to leucotomy. There is probably no true discrepancy; the different findings may well reflect diagnostic difficulties. Where pain is clearly severe hysterical responses are overlooked: where the patient's complaints appear excessive the value judgment of " hysteria " is more often made. In these circumstances the importance of underlying depression, anxiety, or obsessional trends may be underestimated.

Only in one patient (Case 25) was it likely that obsessional features were of major importance: in nine others they played a definite role. Where their presence indicated excessive preoccupation with a relatively mild pain the outlook was correspondingly bright. If, however, obsessional traits complicated a painful state which was in other ways intractable (Cases 22 and 24) they appeared to exert a detrimental influence. All but one (Case 18) of the patients with obsessional traits seemed post-operatively to be less ruminatively preoccupied with their pain. In the majority, obsessional personal habits persisted unchanged.

In six patients paranoid reactions were present. In three they were less marked post-operatively—perhaps through an elevation of mood (Cases 7, 13, and 18)—and in three they became more predominant—perhaps through a reduction of self-control (Cases 10, 12, and 25).

When diffuse or disseminated organic cerebral damage was present pre-operatively it may be presumed that it contributed to the final total organic state. Such organic changes do not necessarily preclude a successful operation (Cases 7 and 10). Three other cases in which cerebral damage was present and which were classified as unimproved or worse (Cases 18, 21, and 24) probably obtained some relief from suffering.

Sex, Age, Duration of Symptoms, and Social Milieu

There were few consistent differences between the results obtained with men and women. At final follow-up the women averaged 29·4 on the combined social rating scale and the men averaged 31·0 points.

Older patients did rather better than younger ones. Twelve patients aged 56 and over averaged 10·3 points of improvement, 13 patients aged 54 and younger averaged only 6·8 points. This may well reflect the fact that less is expected of those who have reached retiring age.

As might have been expected, the longer the duration of the illness the less good was the result. Twelve patients whose illnesses had lasted six years or more averaged 6·8 points of improvement, 13 patients with durations of five years and less averaged 10·0.

Almost all studies of the effects of leucotomy in psychiatric disorders stress the importance of the social environment to which the patient has to return. Where this is favourable, the prognosis is much improved. A similar influence appears in the present series, but as might be expected this variable played a relatively less important role. It is, however, important to consider which aspect of the social milieu bears the main burden of the patient's post-operative condition. If we look at recovery in terms of fitness to resume pre-operative employment, we find that of the 25 cases under review, five were over 64 years old and had retired. However, of these, two were able to resume a fully responsible family role, and one improved to the extent that with support from his wife he was able to enjoy his retirement. Of the 20 patients of employable age, eight were housekeeping, and of these five resumed their home duties, though two functioned at a reduced capacity. Of the 12 patients gainfully employed pre-operatively, five returned to work (four at their original level and one at a reduced capacity). Thus 13 patients were able to return to their previous level of activity, though four of them functioned at a lower level. Of the 12 who failed to do so, four remained at home relatively incapacitated and the condition of eight was such that they were eventually permanently looked after in institutions. Only in one case was this failure due to lack of reasonable cooperation on the part of the family. Of the 17 patients who continued to live at home, 10 (Cases 1, 2, 5, 6, 8, 15, 18, 19, 22, 23) were able post-operatively to resume a life of independence. The remaining seven patients were able to remain at home because of family support, without which they would have needed institutional care.

Only in one case (No. 18) did the patient's post-operative personality defects result in a break-up of the family. This patient suffered with severe spasmodic torticollis, and had inevitably messy eating habits. Some post-operative deterioration in his personal standards greatly distressed his hitherto united family. On the death, one year after his operation, of his wife, always the mainstay of the family, relations between him and his unmarried children deteriorated rapidly and they left home.

He later went to live with his married daughter, where he remained a great trial and a disturbing influence in the home.

Personality Changes

Appreciable damage to frontal lobe tissue will inevitably produce personality changes of greater or lesser degree. The assessment of human values is bound to be subjective, but where the personality pre-operatively is not perfect there is no theoretical reason why these changes should not be an improvement. In at least six of our 25 patients it is not obvious that the changes were on balance unpleasant in character.

In the 16 patients treated with limited operations the personality changes were classified as negligible in two, as slight in six, and as definite in six. Only in two cases were they marked or severe. It is suggested below that in these two cases the damage to frontal tissue may have been greater than planned. In the nine patients treated by extensive operations the changes were classified as definite in two, marked in four, and severe in three. There is thus a close association between the extent of the lesion and the extent of the personality changes.

Morbidity

In addition to the changes of personality which are expected to occur after leucotomy due account must be taken of the operative risk of untoward complications. The present series is small. There were no operative deaths. One patient (Case 1) had a delayed haemorrhage which may have contributed to the excellent results obtained. Two patients (Cases 12 and 14) developed personality changes which were undoubtedly excessive for the modified operations planned. Three other patients developed epileptic attacks.

Meyer and Beck (1954) have shown that with standard leucotomies the amount of damage inflicted is often less than that intended; but we are not aware of any series of pathological investigations which demonstrate how often a modified leucotomy is more extensive than planned. Extrapolation from 25 patients is unjustified, but the present findings are not incompatible with those of other workers, and in particular with those reported by Pippard (1956) from a series of 240 rostral leucotomies. He reports an operative mortality of 1%, an incidence of a further 1% for severe unexpected personality changes, and a figure of 5% for operative haemorrhages of little clinical significance. Pippard states that epilepsy occurs in 5% of cases but that it is exceptional for it to be of any consequence. Freeman in two extensive studies (1953*a* and *b*) concludes that the post-operative epilepsy rate depends largely on the extent of the operation and its nearness to the motor cortex.

Discussion

In the long-term treatment of cases of intractable pain by leucotomy the importance of the extent of the operation in determining the degree of relief obtained has previously been demonstrated in a larger series of cases by, amongst others, the Harvard workers (Bonner *et al.*, 1953) and in France by Petit-Dutaillis *et al.* (1953). The observation that a mild pain is more readily relieved than a severe one is practically a truism. It needs emphasis, however, to offset the tendency to classify intractable pain as either real and severe or neurotic and imaginary. The third main finding that it is the type of psychiatric disturbance, rather than its presence or absence, which is important in determining the outcome of leucotomy for intractable pain has previously been relatively neglected and bears further discussion.

Leucotomy is infrequently called for in the treatment of intractable pain. In Jousse's 118 cases of painful traumatic paraplegia this operation was used only in one case. The result was excellent (Botterell *et al.*, 1954). More recently Fischer-Williams (1956) has reported on the treatment of 77 consecutive patients with complaints of intractable or obscure pain. None of her cases required leucotomy and she concludes that this operation is rarely necessary; however, in several of the cases a variety of other treatments were ineffective. Leucotomy is essentially a treatment for suffering rather than for pain, and it is important to remember that frontal lobe operations relieve only some of the psychological reactions which contribute to suffering. It is important also to remember that other methods of changing the attitude to pain, *e.g.*, electroconvulsive therapy or psychotherapy, may at times be equally effective (Von Hagen, 1957).

It is often impossible to say why one patient with a herpetic root infection develops post-herpetic neuralgia, while another does not. While in most cases it is no doubt a matter of a difference in the severity of the sensations, there will also be other differences related to the vulnerability of the personality.

There is now abundant evidence that leucotomy does not affect the perception of pain and that the immediate autonomic and behaviour disturbances aroused by a novel painful stimulus are, if anything, greater after leucotomy damage. On the other hand, after leucotomy these disturbances are less prolonged and less readily aroused by a threat that the pain experience will be repeated (Elithorn *et al.*, 1955). The chief action of leucotomy, therefore, is to

modify behavioural disturbances which are temporally separated from the provocative insult.

Frequent severe pains produce a common pattern of insomnia, anorexia, weight loss, and depression; but where the pain itself is less severe, the psychiatric picture is more variable, reflects the predominant psychological organization of the patient and determines the character and degree of the disability. Thus the patient who complains of pain may be incapacitated, not directly by the pain, but because he has become depressed, because he is ruminatively preoccupied by his sensations, because he anxiously fears a recurrence of the pain, has anxieties about the significance of the underlying pathology, or fears that he will become incapacitated. He may, if the reaction is an hysterical one, be incapacitated not so much by the anxiety or depression as by his belief in his incapacity. This belief may unconsciously determine symptoms and incapacity greater than physiological limitations determined by the physical lesions.

Leucotomy has two main actions. Like electroconvulsive therapy it has a shock effect which breaks up established moods, particularly of the depressive type. Unlike electroconvulsive therapy it produces a focal and persisting neurological defect which causes changes in the psychological disposition of the patient. The change most frequently reported is a reduction in the tendency to become anxious. It has been suggested in relation to our experimental results that this can be attributed to damage to the mechanisms underlying the formation of anticipatory sets. In effect the perception of a stimulus still gives rise to the concept of a future event but there is a failure to elaborate an emotional state appropriate to this concept. In patients with intractable pain each attack of pain normally carries its own immediate affective connotation and also acts as a warning signal leading to a heightened expectation of further attacks. It is the affective change associated with the awareness of these secondary consequences of a painful stimulus which is reduced by leucotomy.

Normally the affective state aroused by a painful stimulus or the threat of a painful stimulus is an excitatory or anxious one, but, as Russell Davis (1952) has pointed out, the repetition of an excitatory stimulus may lead eventually by a process of habituation to an inhibitory or depressive state. Hence by damaging these mechanisms leucotomy would reduce the ability of the patient to elaborate moods of both anxiety and depression.

The typical post-leucotomy syndrome in cases of intractable pain is thus one in which the patient still makes complaints of severe pain but shows at the same time an affect inappropriately cheerful. Such a syndrome in the absence of an operation and of an objectively demonstrable cause for pain would readily give rise to a diagnosis of hysteria. It might not be meaningless, therefore, to suggest that while leucotomy lessens the individual's propensity to reactions which are anxious or depressive it increases the tendency to reaction of an hysterical type. Such a formulation is not at variance with the observation that our hysterical patients improved. They were, if anything, more hysterical. Their complaints of pain were with one exception unchanged but carried less conviction. One patient (Case 13), post-operatively "just the same", had convinced his wife also that he was no better. On further enquiry, however, she admitted that he now smiled more frequently and never wept. The depth of this patient's hysterical reaction is suggested by the fact that he felt too weak to stir his own tea, and got his wife to do it for him.

The suggestion that frontal lobe damage impairs the ability to elaborate the affect appropriate to the concepts present in consciousness, combined with the fact that in anxiety states and reactive depressions this affective formulation is excessive, would explain the observation reported more than once in the literature (Freeman and Watts, 1950; Hardy, Wolff, and Goodell, 1952) that personality deterioration is less marked in patients operated on for psychiatric reasons than in psychiatrically normal patients leucotomized for intractable pain. In the first case the operation would damage mechanisms which were overactive; in the second they would preoperatively be adequate. In severe hysterics the pre-operative personality suffers already from the primitive nature of the mechanisms underlying emotional elaboration. Hence, although post-operatively the hysteric is more selfish, egocentric, and emotionally labile, the relative may notice little difference. The wife of one patient (Case 9) reported that he was as selfish and as chronic an invalid as ever and that his personality was unchanged. The patient said that he no longer got depressed—otherwise there was no change. More detailed enquiries established that the patient was more and not less selfish than before the operation but had lost some of his ability to implement his policies when opposition was aroused.

In considering cases of intractable pain for leucotomy, therefore, it must be remembered that the pain will not be relieved and that normal people cannot by leucotomy be made inattentive to severe pain unless the operation produces a very definite dementia. Hence the main indication in cases of intractable pain is an excessive psychological reaction of the anxious, depressive, or ruminative type. The more likely it is that the patient is suffering from

severe physical pain, then the less likely it is that leucotomy will help him. Where there is severe organic pain some personality change is essential to the success of the operation. Where a severe hysterical reaction is not secondary to anxiety or depression, the chances of a good result are diminished. Since the risks of either excessive personality change, of post-operative epilepsy, or of operative death amount to about 7%, it is clear that operation is only justified if a direct attack on the pain is impossible and if no other treatment of the psychiatric reaction is practicable.

The treatment of intractable pain, *i.e.*, pain for which the physical cause is beyond treatment, constitutes a problem of the greatest importance to medicine. It is clear that damaging operations on the frontal lobes provide no satisfactory answer. They have some part to play at the present time, but only because of our incapacity to do anything better. These operations do not shield the patient against the recurrence of his pain, but, at the cost of personality changes, interfere with some of the psychological concomitants of physical suffering.

Summary

Twenty-five patients treated for intractable pain by leucotomy-type operations have been followed up for between 18 and 78 months. The results of the operations were assessed by the patient, by the relative most concerned, clinically, and with a rating scale designed to evaluate social adjustment.

Clinical evaluation suggested that 17 of the 25 patients had been clearly helped by the operation. Twenty (80%) showed an overall gain on the social rating. However, only eight (35%) of 23 patients and eight (38%) of 21 relatives thought that the operation had been worth while. (In a larger series of leucotomies undertaken primarily for psychiatric reasons, 75% of 80 patients and 89% of 72 relatives thought the operation had been helpful.) It is concluded that the tendency for patients and relatives to be dissatisfied with a leucotomy for pain is related to the observation that although most patients admitted to some improvement in their symptoms, only five thought that their pains were less intense.

With regard to the type of operation used, the patients, the relatives, and the clinical assessment all reported more favourable results with " extensive" operations than with " limited " ones. In contrast, patients who had " limited " operations tended to show bigger gains on the social rating scales. This discrepancy is related to the fact that while more extensive operations tend to produce greater relief from suffering, they are also more likely to lead to socially crippling defects of personality.

The results of the present study support the following conclusions:

Operations on the frontal lobes—unless they are very extensive—do not impair the subject's ability to perceive and react appropriately to a painful stimulus, but produce relief by impairing his ability to elaborate a persisting attitude or mood.

The probability that leucotomy will provide relief for a patient suffering from intractable pain depends first on the severity of the painful sensations and secondly on the nature of the psychological reaction. Where the pain is not severe and the psychological reaction is largely a depressive or anxious preoccupation with symptoms, the prospects of some degree of relief are high. If pain is severe and frequent, little permanent relief is to be expected. Where hysterical tendencies are present, these may be increased, but since the anxiety which provokes the hysterical symptoms may be reduced, the total change is often a gain in social adaptation.

Operations on the frontal lobe are an unsatisfactory treatment for intractable pain, but if pain cannot be alleviated by other means then in carefully selected cases leucotomy-type operations may produce both relief from suffering and an improved social adjustment.

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A CONTROLLED STUDY OF THE EFFECTS OF LEUCOTOMY

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Previous Studies

Although the operation of leucotomy is now over 20 years old only a few attempts at a controlled assessment of its therapeutic effect have been made (Penrose, 1944; Mettler, 1949, 1952; Friedman, Moore, Ranger, and Russman, 1951; Livingston, 1953; Jenkins and Holsopple, 1953; Freeman, Davis, East, Tait, Johnson, and Rogers, 1954; Jenkins, Holsopple, and Lorr, 1954; Medina, Pearson, and Buchstein, 1954; Powell, 1955; Crandell, Zubin, Mettler, and Kugelmass, 1956). Of these, moreover, a number have suffered from either (*a*) a poor matching of control and treatment groups (*e.g.*, Mettler, 1949; Friedman *et al.*, 1951; Freeman *et al.*, 1954; Powell, 1955) or (*b*) too short a period of follow-up (*e.g.*, Penrose, 1944; Mettler, 1949; Jenkins and Holsopple, 1953; Livingston, 1953; Freeman *et al.*, 1954; Jenkins *et al.*, 1954) so that their validity is suspect. Finally, the conclusions of these studies are conflicting. While intramural improvement is generally reported (Mettler, 1949; Friedman *et al.*, 1951; Jenkins and Holsopple, 1953; Jenkins *et al.*, 1954; Medina *et al.*, 1954) discharge rates are reported as improved by some (Penrose, 1944; Freeman *et al.*, 1954; Friedman *et al.*, 1951), as unchanged (Mettler, 1949; Jenkins and Holsopple, 1953; Medina *et al.*, 1954; Crandell *et al.*, 1956), or even as worse by others (Powell, 1955).

General Principles

A number of possible sources of error must be considered when an attempt is made to assess the therapeutic results of leucotomy. In brief these are as follows:

(1) " Spontaneous remission " has been reported in 30% to 50% of cases in a number of studies of large groups of psychotics (Bond and Braceland, 1937; Hunt, Feldman, and Fiero, 1938; Whitehead, 1938; Guttmann, Mayer-Gross, and Slater, 1939; Stalker, 1939). Where the therapeutic result is not universal and immediate but where, as in leucotomy, a " delayed operative response " is claimed, " spontaneous remission " must be excluded.

(2) Indications for operation may be derived by reviewing improved cases after the treatment. The indications thus derived may in fact be merely general indications of good prognosis, *i.e.*, of " spontaneous remission ". Later cases selected for treatment on the basis of such indications, *e.g.*, a short period of illness, acute onset of symptoms, good premorbid personality, etc., will naturally have a good prognosis and serve to perpetuate the myth of the treatment's success.

(3) It is possible that the severity and outcome of the functional psychoses have changed in the last few decades (Harris and Norris, 1954; Hoenig, Leiberman, and Auerbach, 1956). Comparisons, therefore, of results obtained in the thirties with those after leucotomy obtained in the forties or fifties may not be valid as the cases may not be comparable.

(4) Shorter periods of time may alter the nature of a population to be treated. For example, where the most chronic cases in a hospital are operated upon first, all subsequent series contain more acute material (Scoville, Wilk, and Pepe, 1951) with a naturally better outlook. Later results will improve commensurately.

(5) There are social aspects to " recovery ". The act of treatment may alter a community's attitude and willingness to receive a patient. Many patients have been removed, objectively unimproved, because they " have had the treatment ".

(6) Active treatment may also bias the psychiatrist towards a favourable reassessment of a patient's condition, *e.g.*, increased dementia may be classified as " improvement " because of quieter behaviour.

(7) Finally, a specific treatment, like leucotomy, may be associated with rehabilitative measures which are continued long after the treatment and may be of equal or even greater importance than the treatment itself.

To avoid these sources of error it is necessary:

(*a*) To employ a control group which has the same outlook as the treatment group, contains the same quantities of positive prognostic indicators, and has the same tendency to " spontaneous remission " (see 1 and 2 above).

(*b*) That the treatment and control groups should be treated at the same period of time and as far as possible under the same conditions (see 3, 4, and 7 above).

(*c*) That a long period of follow-up should be undertaken to allow for " flash in the pan " effects due to the enthusiasm of relatives, " total push " measures, mistaken assessments, etc. (see 5, 6, and 7 above).

Arguments for the Proposed Design

Facilities for a forward-looking study of the type proposed by Guttmann *et al.* (1939) and recently undertaken by Ackner, Harris, and Oldham (1957), to examine the efficacy of insulin coma therapy were not available. It was, therefore, necessary to use material already operated upon in a retrospective study, still, however, employing non-leucotomized patients for comparison. It is fundamental, as has been said, that the groups compared should have been treated at the same time and have been of like outlook, so that it could be said at the onset that under similar conditions it would be expected that equal numbers of both groups would recover or improve. The methodological problem resolved itself, therefore, into (1) noting the factors known to affect prognosis, (2) selecting the most important and workable of these, and (3) matching the groups accordingly. It was important that all the data should be as objective as possible as it is difficult to avoid the information that a patient has, or has not, had an operation when working with patients known to the enquirer and with case records available. Data which needed interpretation might become biased in the light of this knowledge. There are three items of completely objective information which are, however, important to prognosis. These are: (1) length of stay in hospital, (2) age on admission, and (3) sex.

(1) **Length of Stay in Hospital.**—The importance of chronicity is shown in Table I which has been constructed from two tables in the Registrar General's (1953) Statistical Review of England and Wales (Mental Health Supplement). The longer a patient stays in hospital the less are his chances of discharge. These, in fact, drop from 1 in 14 after two years to around 1 in 200 after 25 years.

(2) **Age on Admission.**—The effect of age on admission is shown by Penrose (1947). It is clear that the earlier the age of admission the larger the percentage of patients still in hospital at one, five, and 25 years. Even in the young and middle-age groups, where loss of patients through death would not be an important factor, this effect is still apparent and it may be said that the earlier the onset of the illness the worse the prognosis.

(3) **Sex.**—The overall effect of sex on prognosis is not great. There is, however, some unevenness in the chances of discharge in the different sexes after different periods in hospital (Registrar General, 1953).

The Design

The actual method of matching was as follows: Each leucotomy patient was matched with a patient of the same sex, of the same age on admission (in five-year blocks), admitted nearest to the date of admission of the leucotomized patient (in three-month blocks) and still in hospital at the time when the leucotomized patient had the operation. Matching for sex was exact. Matching for age was maintained as closely as possible working backwards in the admission register to obtain patients of the same age but of greater chronicity in the first place, if patients of the same chronicity were not available. Where there was no patient of the same age and the same or greater chronicity, a patient from the next age block was taken, first on the younger side and only if this was not possible from the older side. It will be seen that wherever perfect pairs were not possible the disadvantages have been allocated to the controls if possible. The complete material comprises 396 patients, 198 subjected to leucotomies and 198 controls. This series comprises all patients subjected to leucotomy whose date of admission preceded December 31, 1950. The follow-up continued until December 31, 1955. Twenty of these patients had more than one operation. These are dealt with separately as " multiple leucotomies ". The vast majority of the patients treated had a

TABLE I

CHANCES OF DISCHARGE IN 1949 FROM MENTAL HOSPITAL IN ENGLAND AND WALES BY LENGTH OF ADMISSION IN SURVIVORS*

Period in hospital in years	2—3	3—5	5—10	10—15	15—20	20—25	25—30	+30
Number discharged in 1949	582	482	482	252	120	82	42	66
Number resident on December 31, 1949	7,472	11,745	22,524	21,391	15,697	11,302	9,262	11,799
Number at risk during 1949	8,054	12,227	23,006	21,643	15,817	11,384	9,304	11,865
Chance of discharge—1 in	14	25	48	86	132	139	221	180

*Constructed from M.22, M.29, Registrar General's Statistical Review for 1949, Mental Health Supplement (1953)

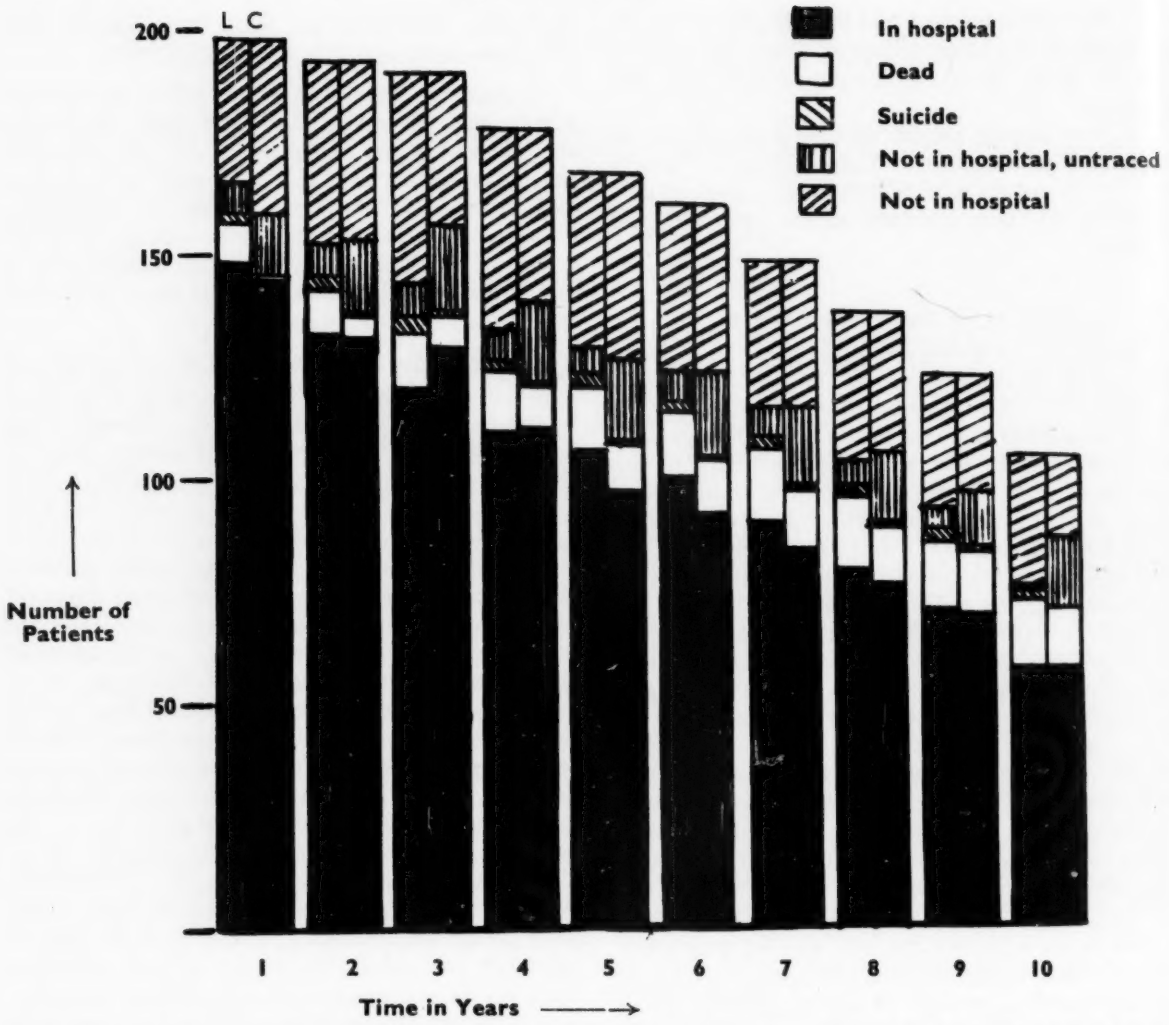

FIG. 1.—Number of leucotomy and control patients in hospital, discharged and traced, out of hospital but untraced, committed suicide or dead, one to 10 years after operation date in groups matched for age, sex, and chronicity.

" standard " leucotomy operation; six patients had orbital undercutting, one a medial undercutting, and one patient transorbital leucotomy.

It will be seen that each patient had a minimum total of five years' observation, taking the periods before and after operation date (range five to 19 years). The period of follow-up after the operation date extended up to 13 years and is illustrated in Fig. 1 which shows the numbers available for different periods of follow-up from one to 10+ years.

It will be seen that the design provides for groups of similar outlook, simultaneous admission to hospital, and prolonged follow-up. The patients subjected to leucotomy will unavoidably have had special conditions for a few months after operation, but apart from this have had no separate programme of treatment.

Statistical Considerations

By and large, inspection is the only statistical method which need be employed, as the results in the two groups, leucotomy and control, resemble each other so closely. Almost all the results presented are, however, amenable to treatment with the χ^2 test and this has been employed with Yates' correction (Fisher, 1936) throughout. Probabilities are shown where there may be some doubt as to the significance of differences on inspection.

Controlled Study of 198 Cases of Leucotomy Matched for Sex, Age on Admission, and Length of Admission

The material studied here comprises all patients subjected to leucotomy (including multiple leucotomies) on admissions up to December 31, 1950,

inclusive and their matched controls. One hundred and ninety-eight pairs have been considered. In each group there were 155 women and 43 men. Each control subject was allocated the operation date of the operated subject with which it was matched in order that the periods before and after operation might be compared. In all the tables where periods of admission to hospital are shown, the length of admission is divided into two periods—less than two years in hospital and more than two years in hospital. It will be seen in the Registrar General's Mental Health Supplement (1953) that 90% of patients discharged from hospital had admission of less than two years' duration. Crandell, Zubin, Mettler, and Logan (1954) found periods in hospital of more than 600 days to be a critical factor in prognosis. This arbitrary division was made roughly to separate the " chronic " from the "acute" patient and to make the tables more readily appreciated on inspection.

Although not matched, it will be seen that the groups compare closely in (1) the number of previous admissions to Runwell Hospital (Table II), and (2) the total period of previous admissions to Runwell Hospital (Table II).

The groups also compare as far as the distribution of diagnoses is concerned, except in two minor categories (Table II). There is a larger number of neurotics and psychopaths in the leucotomy group and only one organic disorder. The position is reversed as far as the controls are concerned where there are more organic disorders than neurotic ailments.

It can be shown that these two diagnostic groups, " organic " and " neurotic and psychopathic ", are drawn from the same area in the pool of cases in this series. The totals of neurotic and organic cases in both leucotomy and control groups are identical (Table II) and the cluster of cases also compares closely in their distribution of ages on admission and in their period from admission to operation date. It was necessary to determine, however, at this stage to what extent the exchange of diagnoses affected outcome in the leucotomy and control groups as a whole. It was conceivable, for example, that all the neurotic subjects would do well and the leucotomy group benefit relatively, or that all the organically ill might die and the control group appear at a disadvantage. In fact, this end of the diagnostic table behaved very similarly in both leucotomy and control groups and the exchange of diagnosis does not have any significant effect on the outcome of the full groups.

The results (Table II) in the 198 pairs may now be considered. It will be seen that leucotomy does not significantly improve the chances of discharge or

TABLE II

PREVIOUS ADMISSIONS, READMISSIONS, DIAGNOSIS, AND RESULTS IN 198 CASES OF LEUCOTOMY AND MATCHED CONTROLS

	Leucotomies	Controls
No. of Previous Admissions to Runwell Hospital		
1	30	29
2	14	14
3	8	7
4	2	3
Total number previously admitted	54	53
Total not previously admitted	144	145
Total cases	198	198
Total Time Spent in All Admissions		
1 mth.	4	10
– 3 mth.	10	5
– 6 mth.	15 (51)	7 (45)
– 1 yr.	10	11
– 2 yr.	12	12
– 3 yr.	2	6
– 4 yr.	1	0
– 5 yr.	0 (3)	2 (8)
–10 yr.	0	0
+10 yr.	0	0
Total previously admitted	54	53
Total not previously admitted	144	144
Total cases	198	198
Diagnosis		
Schizophrenia	91	97
Paraphrenia (paranoid psychosis)	22 (2)	17 (2)
Melancholia (Hypochondriasis) (Affective disorders)	39 (2)	30 (1)
Mania (Affective disorders)	9 (52)	5 (48)
Manic depressive psychosis (Affective disorders)	4	13
Congenital mental defect	2 (16)	6 (19)
Epilepsy	14	13
Neurosis (psychopathic personalities)	16 (3)	7 (4)
Organic disorders	1	10
Total	198	198
(For $n = 5$, $\chi^2 = 13{\cdot}2$, $P = < 0{\cdot}05$)		
(Excluding " organic disorders ": for $n = 4$, $\chi^2 = 4{\cdot}7$, $P = 0{\cdot}5$)		
Results		
Never discharged*	102	113
Transferred to other hospitals	12	5
Total discharged from Runwell Hospital	84	80
Discharged and readmitted to Runwell Hospital†	31	33
Discharged and not readmitted to Runwell Hospital	53	47
Discharged and readmitted to other mental hospitals	11	9
Not readmitted to mental hospitals since discharge	42	38
*Died—same admission	20	19
†Died—subsequent admission	2	4
	22	23
Period from Operation to Discharge (+ transfers)		
1 mth.	10 (3)	19
– 3 mth.	18 (3)	22 (1)
– 6 mth.	11 (1) (65 (9))	13 (69 (2))
– 1 yr.	14 (2)	9 (1)
– 2 yr.	12	6
– 3 yr.	7 (1)	3
– 4 yr.	1 (2)	1 (1)
– 5 yr.	2 (19 (3))	3 (11 (3))
–10 yr.	8	3 (2)
+10 yr.	1	1
Total discharged	84 (12)	80 (5)
(For $n = 1$, $\chi^2 = 2{\cdot}75$, $P = 0{\cdot}1$)		

Table II continued overleaf

TABLE II—*continued*

		Leucotomies	Controls
Period between Discharge and Readmission			
Up to	1 mth.	3	4
	– 3 mth.	4	4
	– 6 mth.	4 (20)	4 (21)
	– 1 yr.	2	4
	– 2 yr.	7	5
	– 3 yr.	1	5
	– 4 yr.	2	3
	– 5 yr.	4 (11)	1 (12)
	– 10 yr.	4	3
	+ 10 yr.	0	0
Total readmitted		31	33
No. of Readmissions to December 31, 1955			
	1	19	16
	2	6	9
	3	5	3
	4	1	2
	5	0	0
	6	0	3
Tota readmitted		31	33
Total Period of Readmission to December 31, 1955			
	1 mth.	2	2
	– 3 mth.	3	5
	– 6 mth.	3 (17)	3 (21)
	– 1 yr.	4	6
	– 2 yr.	5	5
	– 3 yr.	2	0
	– 4 yr.	2	4
	– 5 yr.	1 (14)	0 (12)
	– 10 yr.	8	7
	+ 10 yr.	1	1
Total readmitted		31	33

reduce the number of patients readmitted. Finally, the numbers of deaths in hospital in both groups are comparable. Leucotomy does not accelerate discharge in those patients who leave hospital, neither does it delay readmission in those who return. The number of readmissions and the total period of the readmission to Runwell Hospital are comparable in the leucotomy subjects and controls.

Leucotomy, it is often claimed, improves patients in hospital. Indeed, close perusal of many of the " improved " columns in leucotomy statistics shows most of these patients to be in hospital. This claim has been examined here by assuming that the type of ward in which a patient is resident reflects his behaviour level. The wards were readily classified into three groups: (1) An " open " ward has free access to the grounds, and, whether or not there is a night nurse, caters for patients with the highest level of hospital behaviour. (2) A " non-observation " ward is a locked ward, without a night nurse, however, and is of an intermediate behaviour level. (3) An " observation " ward is a locked ward with day and night staff and caters for patients with the lowest behaviour level.

The normal ward of each patient who was never discharged was noted at the date of operation and again at the date of survey. By " normal ward " is

TABLE III

CHANGES IN WARD ADJUSTMENT OF PATIENTS NEVER DISCHARGED FROM RUNWELL HOSPITAL

Type of Ward	Leucotomies		Controls	
	Ward at Date of Operation	Ward at Date of Survey	Ward at Date of Operation	Ward at Date of Survey
Open	1	7	11	21*
Non-observation	8	17	38	32†
Observation	73	58	45	41‡
Total ..	82	82	94	94

* ($n = 1$, $\chi^2 = 0{\cdot}6$, $P = 0{\cdot}5$)
† ($n = 1$, $\chi^2 = 1{\cdot}47$, $P = 0{\cdot}3$)
‡ ($n = 1$, $\chi^2 = 0{\cdot}12$, $P = 0{\cdot}7$)

meant the ward on which the patient was normally resident before operation, and not the actual ward at the operation date which would, naturally, have been in all leucotomy cases the hospital's surgical ward. The numbers of patients on each type of ward is thus shown (Table III) for leucotomy subjects and controls before and after operation. The period after operation varies as the survey date was fixed (December 31, 1955) while the operations were spread over a long period. The initial distribution of wards is significantly different in the two groups, but it must be remembered that matched pairs are no longer being considered, merely two subgroups of non-leucotomized patients in the fully matched groups. In both leucotomy subjects and controls there is a general trend towards improvement. Patients in observation wards become fewer and those in open wards increase in number. The rate of improvement does not differ significantly between the two groups. A more detailed study of ward adjustment was made in undischarged patients subjected to a single leucotomy and their controls. Table III shows the general position of the two groups (leucotomized and non-leucotomized) at two dates, before and after operation. Individual patients within the groups may have remained the same, deteriorated, or improved, and it was possible that significant movements in opposite directions had cancelled themselves out in the final table. As far as the patients on closed wards before operation were concerned, there was a sufficient number of cases to determine what in fact did happen to make the final result. These patients might remain in closed wards, improve one step (to non-observation wards) or, finally, two steps (to open wards). The proportion of patients improving in the leucotomy and control groups is the same (Table IV). In patients resident in non-observation wards before operation the figures are smaller (Table IV), and while it may appear that the controls do better than the patients subjected to leucotomy this result must be treated with caution. In general, however, the previous

TABLE IV

WARD AT TIME OF SURVEY OF PATIENTS NOT DISCHARGED IN (A) CLOSED AND (B) NON-OBSERVATION WARDS AT DATE OF OPERATION

	Type of Ward	Leucotomy	Controls	Total
A	Open	4 (6·5%)	5 (12·5%)	9
	Non-observation	14 (22·5%)	6 (14·5%)	20
	Observation	45 (71%)	30 (73%)	75
	Total	63	41	—
	($n = 2$, $\chi^2 = 1{\cdot}7$, P = not significant)			
B	Open	2 (25%)	8 (25%)	10
	Non-observation	2 (25%)	22 (66%)	24
	Observation	4 (50%)	3 (9%)	7
	Total ..	8	33	—
	($n = 2$, $\chi^2 = 8{\cdot}2$, P = $<0{\cdot}05$)			

finding that leucotomy does not improve ward level is fully borne out.

Finally, the death roll has been considered in more detail and it is shown that the diagnostic distribution of the dead is comparable in the leucotomized patients and controls as is the age distribution of the dead (Table V). The number of leucotomized patients dying within six months of operation is not significantly greater than the number of controls, but it must be added that the number of " delayed operation deaths " (McLardy, 1950) which might be expected from 200 patients would be small (about four to six).

A histogram (Fig. 1) has been constructed to show the position of patients one to 10+ years after the operation date. The patients are shown as (1) resident in a mental hospital, (2) discharged and contacted, (3) discharged and not contacted but not resident in the same name in a mental hospital, and (4) dead. The similarity in the two groups is self evident.

TABLE V

DEATHS AND AGE AT DEATH OF PATIENTS DYING IN RUNWELL HOSPITAL

Diagnosis	Leucotomies	No. at Risk	Controls	No. at Risk
Deaths				
Schizophrenia	4	91	7	97
Manic depressive psychosis	10	52	6	48
Paraphrenia	4	22	2	17
Congenital mental defect	0	3	1	5
Epilepsy	1	14	5	13
Neurosis (psychopathic personalities)	2	16	0	7
Organic disorders	1	1	2	11
Died within 6 mth. of operation date	9	—	3	—
Deaths in patients never discharged from hospital	20	—	19	—
Age at Death				
21–30	3	—	4	—
–40	4	—	3	—
–50	8	—	6	—
–60	5	—	7	—
+60	2	—	3	—

To summarize, therefore, 198 patients treated by leucotomy when compared with a matched series of non-leucotomized patients do not have (1) improved chances of discharge from hospital, (2) an accelerated discharge, (3) reduced chances of readmission, (4) a delayed readmission, (5) a reduced number of readmissions, (6) a reduced total period of readmission, (7) improved hospital behaviour as judged by ward level, or (8) a significantly increased death rate.

Controlled Study of 20 Cases of Multiple Leucotomy Matched for Sex, Age on Admission, and Length of Admission

Patients treated with more than one leucotomy, or " multiple leucotomy ", have been included in the group of 198 cases described above.

The patients undergoing multiple leucotomies and their controls have been treated in exactly the same way as has already been described for all leucotomies. It so happens that only female patients were concerned. The control patient was matched in each case, as far as operation date is concerned, with the first operation. Detailed tabular results are not given. When examined separately, the results in all respects are similar to the results already reported. It can now be added that having more than one leucotomy does not improve the patient's prospects in comparison with untreated controls.

Controlled Studies of 43 Male and 135 Female Cases of Single Leucotomy Matched for Sex, Ages on Admission, and Length of Admission

Detailed tabular results are not given. The method, results, and conclusions are as previously found. Sex appears to have no influence on the results of leucotomy.

A Comparison of " Recovered " Patients

It will be seen that 80 patients—42 leucotomized, 38 controls—having been discharged from hospital have not since been readmitted to Runwell or any other mental hospital in England and Wales under the same name. These have been designated " recovered " patients, and one control, who was not readmitted, having committed suicide, had to be excluded. Comparisons between the leucotomy and control " recoveries " have been made (Table VI *et seq.*).

The level of recovery is compared, but the comparison is marred by the larger number of untraced cases in the control series. Experience has shown that untraced patients later traced (between

TABLE VI

WORK AND SYMPTOM STATUS OF PATIENTS DISCHARGED AFTER OPERATION AND NOT SUBSEQUENTLY READMITTED (" RECOVERED PATIENTS ")

	Leucotomies	Controls
Work Status		
As competent as before illness	14	18
Coping	20	4
Incompetent or idle	5	0
Not contacted	3	15
Total	42	37
Symptom Status		
No symptoms	15	18
Symptoms better	18	2
Symptoms same	6	2
Symptoms worse	0	0
Not contacted	3	15
Total	42	37

TABLE VII

DIAGNOSIS OF ALL PATIENTS DISCHARGED AFTER OPERATION AND NOT SUBSEQUENTLY READMITTED TO MENTAL HOSPITAL (" RECOVERED PATIENTS ")

Diagnosis	Leucotomies		Controls	
	Recovered	No. at Risk	Recovered	No. at Risk
Schizophrenia	14	91	10	97
Affective disorders	15	52	14	48
Paraphrenia	5	22	3	17
Epilepsy: mental defect	3	16	1	19
Psychoneurosis: Psychopathy	5	16	5	7
Organic brain disorders	0	1	4	10
Total	42	198	37	198

TABLE VIII

AGE ON ADMISSION AND LENGTH OF ADMISSION TO OPERATION OF ALL PATIENTS DISCHARGED AFTER OPERATION AND NOT SUBSEQUENTLY READMITTED (" RECOVERED PATIENTS ")

	Leucotomies	Controls
Age on Admission		
−20	3	1
−30	8	10
−40	10	11
−50	12	4
−60	7	10
+60	2	1
Total..	42	37
(For $n = 2$, $\chi^2 = 3{\cdot}9$, $P = 0{\cdot}2$)		
Length of Admission to Operation Date		
− 1 mth.	12	8
− 3 mth.	2	6
− 6 mth.	2 (23)	6 (31)
− 1 yr.	4	7
− 2 yr.	3	4
− 3 yr.	6	2
− 4 yr.	4	1
− 5 yr.	4 (19)	0 (6)
−10 yr.	5	3
+10 yr.	0	0
Total	42	37
(For $n = 1$, $\chi^2 = 1{\cdot}5$, $P = 0{\cdot}2$)		

January, 1956, and July, 1957) tended to be doing well as far as work and symptoms were concerned. Indeed, they had lost contact with the hospital as support was no longer needed. On the other hand, it is possible that the untraced patients may be dead or, in the case of the younger single women, married and admitted to a mental hospital in another name. The death rates in the two groups are so comparable as far as the patients traced are concerned that it is difficult to believe that a large number of the untraced controls can be dead. The number of eligible women is small and, as it were, three disasters have to be assumed for patients to be lost in this second way. First, marriage; second, readmission; and finally, insufficient interest by the psychiatrist in the patient's previous illness treated in Runwell for a request to be made for her case record or for a report. A record is kept of such enquiries and some patients were traced in this way.

It can be seen, however, that both as far as work status and symptoms (Table VI) are concerned (even excluding the untraced patients) the level of the controls already matches that of the leucotomized patients in the best adjusted categories. As, therefore, similar numbers recover to roughly the same extent, it is of great interest to know whether similar patients are involved in the recoveries. The distribution of diagnosis is very similar indeed (Table VII), as is the age distribution and the length of stay before the operation date (Table VIII).

Finally, of the 42 " recovered " leucotomy patients, 13 were discharged more than two years after operation, some of these five to 10 years after operation. Six controls were discharged more than two years after the operation date (for $n = 1$, $\chi^2 = 0{\cdot}7$, $P = 0{\cdot}3$). To sum up, similar patients recover after leucotomy in similar numbers to those who recover in a matched control group not so treated. The number of controls who make delayed responses is not significantly different from the number of patients subjected to leucotomy and there is thus no evidence for a delayed operative response. In fact, these responses seem likely to be spontaneous remissions.

Summary

The results in 198 cases treated by leucotomy were compared with those in 198 controls matched for chronicity, age on admission, sex, and under treatment at the same time.

Leucotomy did not appear to (*a*) improve the chances of discharge from hospital; (*b*) accelerate

discharge; (*c*) reduce the chances of readmission; (*d*) delay readmission; (*e*) reduce the number of readmissions; (*f*) reduce the total period of readmission; (*g*) improve hospital behaviour as judged by ward level; (*h*) significantly increase the death rate.

A second leucotomy did not significantly improve the patients' prospects of discharge in relation to the controls.

The sex of the patients did not influence the results of leucotomy.

" Recovered " patients had at least the same level of adjustment in the control group as in the leucotomy group and seemed similar in that they showed the same distribution of diagnoses, ages, and lengths of stay.

No evidence was found for a delayed operative response after leucotomy.

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THYROTOXIC MYOPATHY

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It has long been recognized that there is a connexion between the function of the thyroid gland and muscular strength.

Both Graves (1835) and von Basedow (1840), in their original studies, called attention to muscular weakness as an important symptom in thyrotoxicosis. This weakness is usually localized to the proximal muscle groups, primarily to the lower extremities, and is manifested in difficulty in going up and down stairs and in arising from a sitting position. In its milder forms this muscular weakness is a common symptom, although it is perhaps rarely noted in the case history and examination, being instead attributed to general asthenia. In a more advanced form, including pronounced paresis and atrophy, the symptom seems to be less common. About 40 such cases are described in the literature under the title of chronic thyrotoxic myopathy.

In 1955, two cases of so-called chronic thyrotoxic myopathy were treated in this hospital. Taking these two cases as the point of departure, we have undertaken a more systematic investigation of the musculature in thyrotoxicosis and have thus far examined 20 patients. The investigations included, in addition to the routine clinical examination procedures and functional tests, electromyography, and studies of biopsy specimens from the muscles. The following is a report of the series investigated, the methods used, and the results obtained, as well as a discussion of the observations.

Materials and Methods

Material.—The material comprised a series of 20 patients. Eleven (Cases 1 to 11) presented pronounced symptoms of either atrophy or muscular weakness. Ten of these patients (Cases 1 to 10) suffered a high grade of disability. The clinical picture in these 10 cases agreed completely with the condition described as chronic thyrotoxic myopathy. In Cases 12 to 20 the atrophy and muscular weakness was only slight or moderate. Table I shows the sex and age distribution in the series.

The diagnosis of thyrotoxicosis was established on the basis of both the clinical picture and the results of prevailing examining methods such as tracer iodine studies, determination of protein-bound iodine in serum, basal metabolism, serum cholesterol, and the 24-hour excretion of creatine in urine. In all cases the diagnosis was also confirmed by the results of the treatment.

Methods.—In the tracer iodine tests (0·08 m.c. iodine^{131} by mouth) the uptake in the thyroid gland after three and 24 hours and the excretion in the urine during the first 24 hours were determined. The approximate normal limits taken were 50% for the uptake in the thyroid gland after 24 hours and 30% for excretion in the urine during the first 24 hours. The protein-bound iodine in serum was determined according to the method of Barker, Humphrey, and Soley (1951). A value of 4 to 8γ% was considered as normal.

Creatine and creatinine were determined according to Folin (1904).

In the glucose tolerance test the patients received 1 g. glucose per kilogram of body weight by mouth, and the blood sugar was determined after 30, 60, 90, 120, 150, and 180 minutes.

For the electromyographic examination concentric needle electrodes were used (platinum wire 0·20 mm. in diameter, insulated from a cannula of stainless steel having an outer diameter of 0·5 mm.). The action potentials were led off to a differential amplifier (time constant 30 m.sec.) connected to an oscilloscope which recorded the time in milliseconds or 1/100 second. The output of the amplifier was also fed to a loudspeaker. Measurements from tracings were made in all cases.

All the patients were examined with electromyography (E.M.G.). In three cases only the gluteal muscles were examined. In all these cases changes were found which were characteristic of myopathy. A similar picture—patchily distributed areas from which a large number of rapid diphasic and polyphasic potentials were recorded—was, however, also observed in two patients suffering from duodenal ulcer and in one patient with acute nephritis. Neither of these three patients had any symptoms or signs of thyrotoxicosis nor were the gluteal muscles paretic. Because of these findings the activity from the gluteal muscles was not recorded in the remaining 17 cases with thyrotoxicosis. In 17 patients the quadriceps muscles on both sides were examined, in seven cases also the deltoid muscles. The muscles were systematically searched, the point of the needle, inserted in several different areas, being moved from superficial to deeper parts of the muscle.

TABLE I
VALUES FOR THYROID FUNCTION

Case No.	Sex and Age	I^{131} Accumulation in Thyroid (%)	Protein-bound Iodine (γ%)	B.M.R.	Creatine Excretion (mg./24 hr.)	Duration of Symptoms (yr.)	Muscular Weakness		Atrophy	
							Upper Extremity	Lower Extremity	Upper Extremity	Lower Extremity
1	F 48	72	24·5	+22	435	1½	++	+++	++	+++
2	M50	70	21·5	+77	689	2	++	+++	++	+++
3	F 61	—	28·0	+56	410	3	++	+++	++	+++
4	F 54	—	16·0	+50	440	3	++	+++	++	+++
5	F 61	61	7·0	+42	200	2	++	+++	++	+++
6	F 70	80	7·5	+48	640	15	+++	+++	+++	+++
7	M51	74	9·4	+21	96	1	+++	++	+++	+++
8	F 67	69	10·5	+32	310	3	++	+++	++	+++
9	M67	65	11·6	+29	200	6	+++	++	+++	++
10	F 66	76	8·9	+80	600	4	+++	+++	+++	+++
11	M55	69	11·2	+59	430	1	++	++	+++	++
12	M60	59	19·0	—	100	1	++	++	++	++
13	F 45	60	12·0	+32	1,224	½	+	++	+	++
14	F 47	78	11·0	+60	570	½	0	+	0	+
15	F 37	70	12·8	+36	0	½	0	+	0	0
16	F 61	60	9·2	+44	0	1	0	+	0	+
17	F 54	73	16·0	+46	730	1	+	+	+	+
18	F 66	68	8·6	+23	0	1	0	+	0	0
19	F 39	79	8·9	+33	1,240	½	0	+	0	+
20	M38	—	29·0	+88	520	½	0	+	0	+

\+ = slight
++ = moderate
+++ = considerable

Muscle tissue was examined histologically in 18 cases. The biopsy material was taken from the quadriceps muscle in 12 cases, from the gluteus maximus in four, from the supraspinatus in one, and from the extensor musculature of the forearm in one.

The excised muscle tissue was fixed in 10% formalin solution or in Bouin's fluid. In two cases basic lead acetate was used as well. The preparations were stained with eosin and haematoxylin and according to van Gieson's method. Those fixed in basic lead acetate were stained with toluidine blue solution.

Results of the Investigation

Age and Sex Distribution.—In Cases 1 to 10 the age ranged between 48 and 70 years. This group included seven women and three men. In Cases 11 to 20 the ages lay between 37 and 66 years, and the group comprised seven women and three men.

Signs of Thyrotoxicosis.—Thyrotoxic eye symptoms were entirely absent in Cases 1 to 10. In three patients (Cases 1, 6, and 7) finger tremor was also absent. On the other hand, tachycardia was found in all cases. An appreciable loss of weight, ranging from 20 to 30 kg., was observed. In Cases 11 to 20 thyrotoxic eye symptoms were more or less pronounced in all but two cases (14 and 16), and finger tremor was present in all cases. The duration of the symptoms in Cases 1 to 10 varied between one and 15 years. In seven cases the symptoms had been present for more than three years and in only three cases for shorter periods. In Cases 11 to 20 symptoms had been apparent only six months to one year. The laboratory values obtained for the function of the thyroid gland are presented in Table I.

Muscular Weakness and Atrophy.—In all except Case 7 the muscular weakness was localized mainly to the proximal muscle groups. In six patients (Cases 1, 2, 3, 4, 5, and 8) the weakness was principally localized to the lower extremities. These patients were unable to go up and down stairs or to arise from a sitting position. They were not even able to walk on level ground without assistance. In Cases 6, 7, 9, and 10 there was pronounced weakness in the upper extremities as well. Patients 6 and 10 were able only with the greatest difficulty to raise the arms above the horizontal plane, and patient 9 was only able to abduct the arms about 30 degrees. Patient 7 was unable to raise his arms at all and differed otherwise from the other patients in that he had pronounced weakness in the hands and fingers as well. The muscular weakness in Case 7 started proximally as in the other cases, however, and only later did the peripheral paresis occur. Patient 6 had paresis even in the pharyngeal musculature and in both sternomastoid muscles. Two patients (Cases 8 and 10) had earlier been admitted to nursing homes because of pronounced muscular weakness. One patient (Case 6) had received an invalid's pension because of the muscular symptoms. Two patients (Cases 1 and 5) had previously been interpreted as hysterical disturbance of walking. Patients 11 to 20 had only slight to moderate muscular weakness, localized principally to the lower extremities. In three patients (Cases 3, 4, and 5) the muscular weakness started before other signs of thyrotoxicosis were observed.

The atrophy was most pronounced in the quadriceps and the gluteal musculature, but in five cases

appreciable atrophy was observed in the musculature of the shoulder and upper arm as well. In Case 6 there was also marked atrophy of both sternomastoid muscles. Table I gives the localization of the muscular weakness and atrophy as well as the duration of both muscular and other thyrotoxic symptoms.

Neurological Investigation.—In three patients (Cases 1, 4, and 5) both knee and ankle jerks were absent, in one (Case 3) only the ankle jerks. Otherwise the neurological examination showed normal conditions in all cases.

Carbohydrate Metabolism.—Before treatment two patients (Cases 1 and 2) presented signs of diabetes with elevated fasting blood sugar levels and glycosuria. Three patients (Cases 3, 8, and 10) had diabetic glucose tolerance curves.

Electromyography.—In the 17 cases in which the quadriceps and the deltoid muscles were examined every muscle explored showed in different areas one to several spots in which 75 to 100% of the recorded potentials were diphasic with a duration of 1 to 4 milliseconds and polyphasic with a duration of 3 to 6 milliseconds. The polyphasic potentials would in several cases best be described as " notchy diphasic ". The amplitude varied between 100 microvolts and 3 millivolts, the lowest voltages being observed in considerably atrophic and weak muscles. On maximal contraction a " dense " or " scanty " interference activity was recorded, depending on the degree of paresis: a greater number of different potentials was led off from stronger than from weaker muscles. No statistical analysis of the mean duration of the potentials was made.

Fig. 1 (Case 15) shows the activity from such an abnormal area in a slightly paretic quadriceps muscle. In *A* is seen the activity on a moderate contraction. Seventy-five per cent. of the potentials were notchy diphasic (*B*), polyphasic (*C*), and diphasic of abnormally short duration (*D*).

The potentials in Fig. 2 (Case 12) were led off from a moderately weak quadriceps muscle. *A* shows the pattern on a weak contraction. No potentials with a duration above 5 milliseconds could be observed with the needle in this spot, only diphasic (*B* and *C*) with a duration of 2 to 2·5 milliseconds, triphasic (*D*) and polyphasic (*E*) at 3·5 to 4 milliseconds. The amplitude varied from 1 to 3 millivolts.

The records from a conspicuously atrophic and moderately paretic deltoid muscle are seen in Fig. 3 (Case 11). In *A* the activity on a weak contraction is illustrated. No " normal " potentials could be led off from this particular area, only notchy diphasic (*B*), polyphasic (*C* and *D*), and rapid diphasic (*E*).

In one patient (Case 6) both sternomastoid muscles were highly atrophic and paretic. On maximal contraction of the right sternomastoid muscle (Fig. 4) an interference activity was seen (*B*). No di- or triphasic potentials with a duration above 4 milliseconds could be observed in this muscle, but only di- or triphasic with a duration of 1·5 to 2 milliseconds (*C*, *D*, and *E*) and polyphasic at 5 milliseconds (*F*). The amplitude did not exceed 200 microvolts.

In none of these cases were fibrillations observed.

Two patients (Cases 5 and 7) showed a dissimilar electromyographic picture. From the quadriceps muscles of one of these patients (Case 7) a pattern was seen which was quite characteristic of myopathy, with scattered areas from which a considerable number of rapid diphasic and polyphasic potentials were recorded. The activity of the extensor muscles of the forearms and of the first interosseus muscles of the hands was, on the other hand, without any doubt consistent with a lesion of the peripheral motor neurones: only single discharges of diphasic action potentials with a duration of 6 to 7 milliseconds and an amplitude of 2 millivolts were recorded. The frequency on maximal contraction was 30 per second. Fibrillary action potentials were found in all the muscles examined in large numbers, thus also in the quadriceps muscles. In Fig. 5 are shown the activity of the extensor muscles of the right forearm on maximal voluntary contraction (*A*), spontaneous fibrillations (*C*), and sharply rising positive potentials (*D*) from the same muscles (Kugelberg and Petersén, 1949; Jasper and Ballem, 1949).

The other patient (Case 5) showed a considerable weakness of the quadriceps muscles. On voluntary contraction only polyphasic action potentials were recorded, the duration varying from 3 to 6 milliseconds and the amplitude between 500 microvolts and 2 millivolts. The frequency was not higher than 8 per second. Fibrillation potentials as well as sharply rising positive potentials (Fig. 6, *A*, *B*, and *C*) were observed in all regions of the muscles. It is somewhat difficult to interpret this pattern: it may equally be the expression of a myopathy as of a neurogenic disorder.

Histological Examination.—The histological examination of the musculature was entirely negative in one patient (Case 20). In the other 17 cases investigated histologically it showed widely varying degrees of atrophy of the muscle fibres. In seven patients (Cases 2, 3, 4, 6, 7, 8, and 19) there was an increase in the number of sarcolemmal nuclei, sometimes diffusely, sometimes only in spots. In some of the muscle specimens studied the nuclei formed

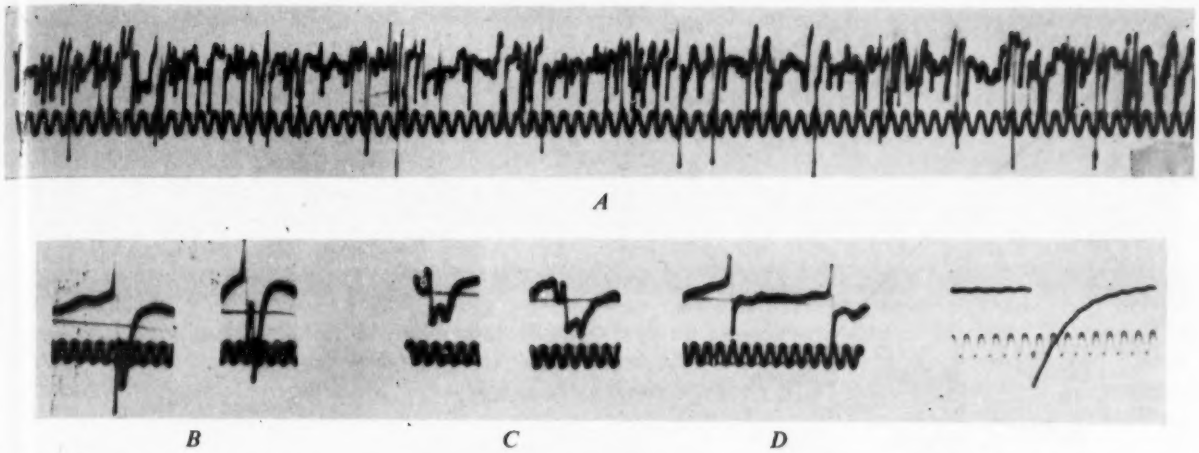

FIG. 1.—Records from a slightly paretic quadriceps muscle. Calibration 1 millivolt. *A*. Moderate contraction gives rise to a scanty interference activity (time, 1/100 sec.). *B-D*. Detailed pictures of different potentials. In this and the following records the duration of the potentials is shown in parenthesis. *B*. Notchy diphasic (5 m. sec.). *C*. Polyphasic (5 m.sec.). *D*. Diphasic (1 m.sec.). Time, 1/1,000 sec.

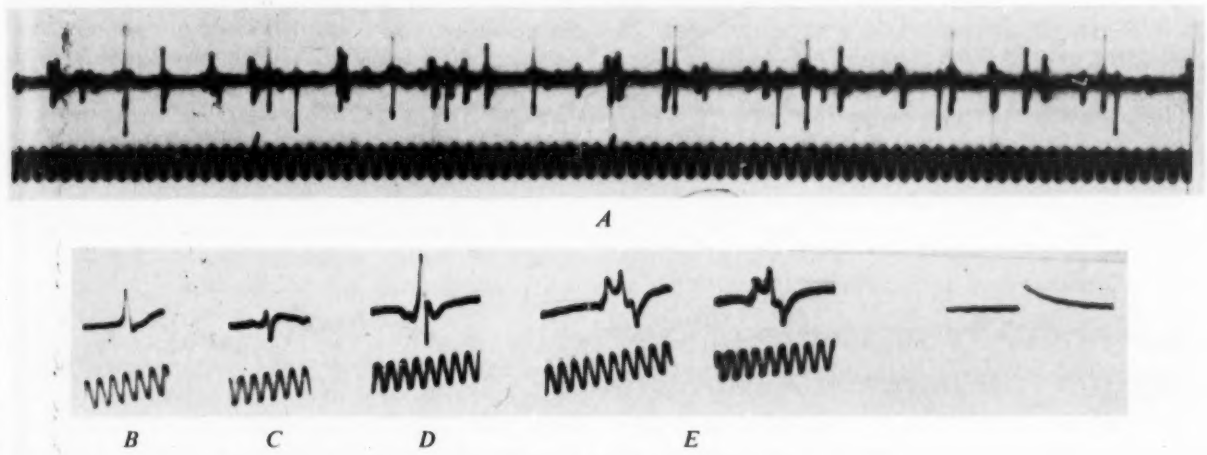

FIG. 2.—Records from a moderately paretic quadriceps muscle, Calibration 1 millivolt.
A. Weak contraction (time, 1/100 sec.). *B-E*. Detailed pictures of different potentials. *B*. Diphasic (2 m.sec.). *C*. Diphasic (2·5 m.sec.). *D*. Triphasic (3·5 m.sec.). *E*. Polyphasic (4 m.sec.). Time, 1/1,000 sec.

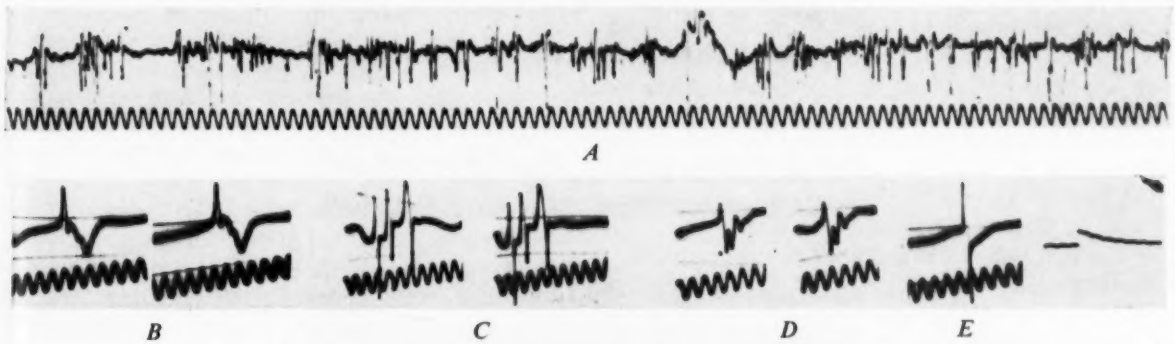

FIG. 3.—Records from a considerably atrophic and moderately paretic deltoid muscle. Calibration 100 microvolts.
A. On a weak contraction single discharges of different potentials with varying frequency are recorded. Time, 1/100 sec.
B-E. Detailed pictures of different potentials. *B*. Notchy diphasic (4 m.sec.). *C*. Polyphasic (5 m.sec.). *D*. Polyphasic (3·5 m.sec.). *E*. Diphasic (2·5 m.sec.). Time, 1/1,000 sec.

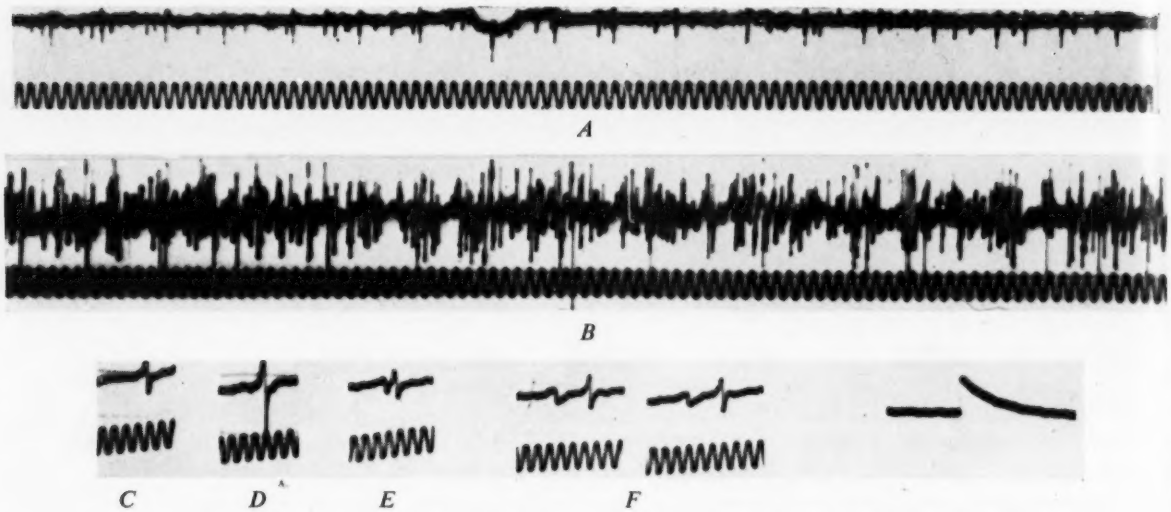

FIG. 4.—Records from a conspicuously atrophic and paretic sternomastoid muscle. Calibration 100 microvolts. *A*. Weak contraction. *B*. On strong voluntary contraction an interference activity is led off. Time, 1/100 sec. *C-F*. Detailed pictures of different potentials. *C*. Diphasic (1·5 m.sec.). *D*. Diphasic (2 m.sec.). *E*. Triphasic (2 m.sec.). *F*. Polyphasic (5 m.sec.). Time, 1/1,000 sec.

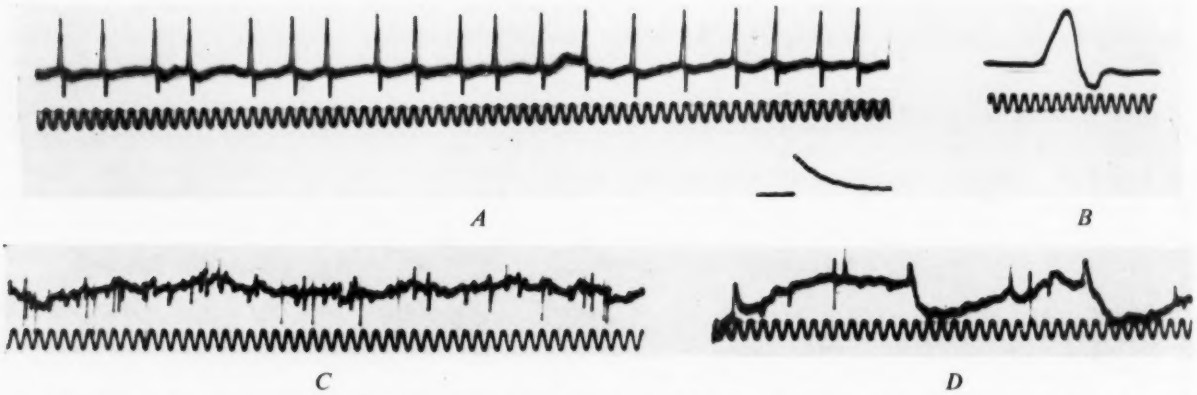

FIG. 5.—Activity from extensor muscles of the right forearm indicating a partial denervation. Calibration in *A* and *B* 1 millivolt. *A*, maximal voluntary contraction gives rise to high amplitude single discharges. Detailed picture of action potential (7 m.sec.) in *B*. *C*. Spontaneous fibrillation activity. *D*. Fibrillations and sharply rising positive potentials.

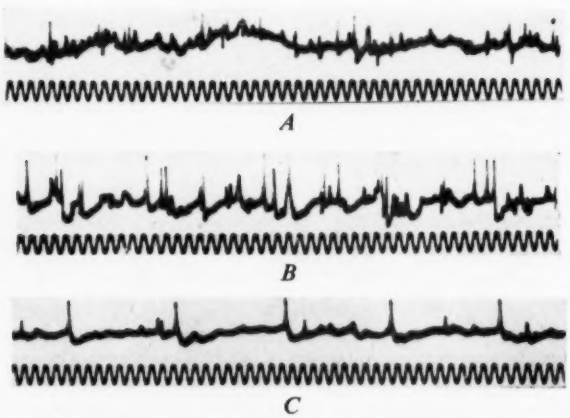

FIG. 6.—Involuntary activity from the right quadriceps muscle. Fibrillation activity and sharply rising positive potentials immediately after insertion of the needle (*A*); five seconds later (*B*); 10 seconds later (*C*).

continuous rows or small conglomerates. In two patients (Cases 7 and 19) an appreciable swelling of the sarcolemmic cells was observed. In five patients (Cases 2, 4, 6, 11, and 19) thin, basophilic muscle fibres with densely packed nuclei were a characteristic feature of the picture. The number of such muscle fibres varied from case to case. In only four patients (Cases 3, 4, 6, and 8) obliteration of the cross striation and a more or less distinct waxy degeneration were observed. In addition, in one patient (Case 6) a breakdown of isolated muscle fibres was demonstrated. As a whole, necrobiotic changes in the musculature were very slight or entirely absent. In two patients (Cases 3 and 8), however, relatively large necroses were observed in the musculature. In Case 3 the necrotic regions presented comparatively abundant inflammatory cells and so-called myocytes (Fig. 7). In Case 8 new connective tissue and an accumulation of iron-pigment-loaded phagocytes were observed as well in connexion with the necrosis (Fig. 8). An observation common to these two cases was the hyalinized muscle fibres and greater or lesser conglomerates of nuclei in the margin of the necroses (Fig. 9). Such nuclear conglomerates were found to a slight extent in two other patients (Cases 4 and 19). In some patients (Cases 3, 6, 8, and 11) small accumulations of lymphocytes, resembling those occurring in myasthenia gravis, were seen in the interstitial tissue (Fig. 10). No increase in adipose tissue in the musculature of a magnitude having pathological significance was observed.

In a number of cases the biopsy material included minor nerves. Only in Case 7 changes of single nerves were observed in the form of demyelinization and vacuolization; the biopsy specimen was taken from the extensor musculature of the forearm.

Treatment.—In all cases muscular strength improved appreciably after two months' treatment of the thyrotoxicosis. To a certain extent Case 7 was an exception. Even in this patient the proximal muscular weakness disappeared after two months' treatment, but the peripheral paresis in the hands and fingers had not disappeared until after an additional five months. In all cases muscular strength was fully restored with the exception of Case 6, in which the patient died of cholangitis before completion of the treatment.

Electromyograms during the course of treatment showed a decrease in rapid diphasic potentials, but the number of polyphasic potentials seemed to be unchanged.

Discussion

It is evident from the foregoing report that clinical signs of thyrotoxicosis were but slight and thyrotoxic eye symptoms entirely absent in the 10 patients with crippling paresis. In consequence, the diagnosis in these cases was not established until after the disease had been in progress for several years, and in one patient (Case 6) only after a period of 15 years. In the mild cases (11 to 20), on the other hand, thyrotoxic eye symptoms were present in all except two, and the duration of the symptoms was only from six months to one year. It seems probable, judging from our material, that the existence of thyrotoxicosis for a long period without treatment is one of the main factors in the origin of disabling thyrotoxic myopathy. It is therefore natural that the mean age of the patients with crippling paresis in our series should be high inasmuch as thyrotoxicosis in older persons frequently presents with an atypical clinical picture and is therefore difficult to diagnose.

In contrast to the reports in the literature, where chronic thyrotoxic myopathy is said to be considerably more common in men than in women, our 10 severe cases show a sex distribution largely the same as that for thyrotoxicosis in general, *i.e.*, seven women and three men. In the series of 10 mild cases (11 to 20) as well, the sex distribution was the same, seven women and three men.

In some of the patients the muscular weakness began several years before definite thyrotoxic symptoms were observed. The weakness and atrophy in six of Cases 1 to 10 was primarily localized to the proximal muscles in the lower extremities, in four cases to the upper extremities as well. In one patient (Case 7) there was distal muscular weakness and atrophy in addition to proximal. Electromyography in this case showed a typical neurogenic picture in the peripheral muscle groups but myogenic in the proximal muscles. As in the other cases the paresis first appeared proximally and only later peripherally. When treatment was instituted, the paresis in the proximal muscle groups disappeared very quickly while that in the peripheral persisted much longer. In this case neuropathy was probably present as well as myopathy. Whether or not thyrotoxicosis can give rise to both myopathy and neuropathy cannot of course be established definitely on the basis of this case alone. It is possible, however, that neuropathy has occurred in other cases; areflexia in cases from the literature as well as in our own material supports this assumption.

Whether or not the impaired carbohydrate metabolism in five cases has any pathogenetic significance in the origin of the paresis or if it is only an expression of the duration of the thyrotoxicosis cannot be determined.

Pathological creatinuria has been pointed out in the literature as a constant and typical observation

FIG. 7.—Case 3: Necrotic region of muscle with collections of "myocytes". × 1,100.

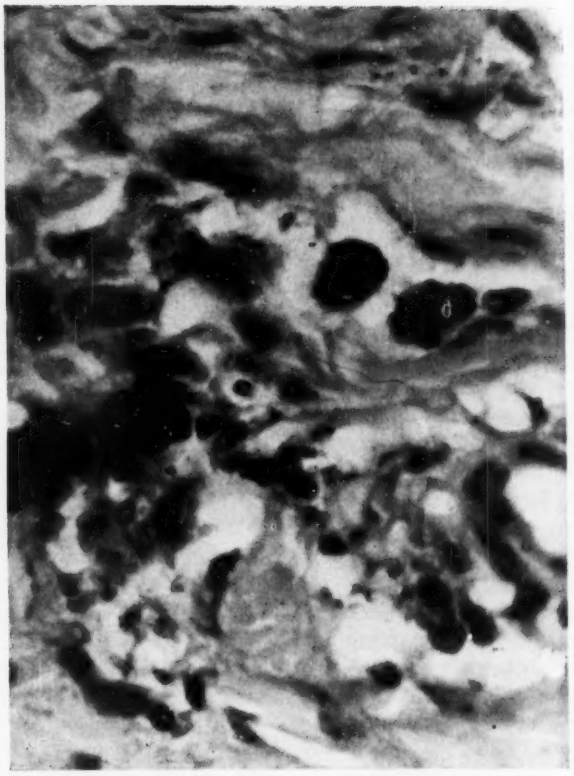

FIG. 8.—Case 8: Muscle with newly-formed connective tissue in necrotic area. Some phagocytes loaded with iron pigment are seen × 1,100.

FIG. 9.—Case 3: Necrotic region of muscle with conglomerates of nuclei in the margin of the necrosis. × 1,100.

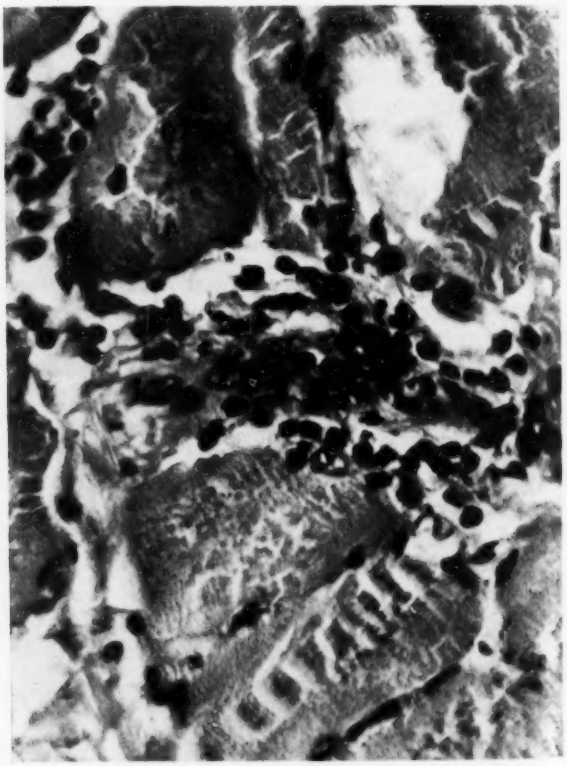

FIG. 10.—Case 6: Muscle with small accumulation of lymphocytes, resembling those occurring in myasthenia gravis. × 625.

in thyrotoxic myopathy. However, Zierler (1951) found only inappreciable spontaneous creatinuria in his cases but extremely pathological tolerance values. He interprets this as being due to reduced creatine synthesis in the liver. All our cases of chronic thyrotoxic myopathy, however, presented definitely pathological spontaneous creatinuria. On the other hand, there was no parallelism between the quantity of creatine excreted in the urine and the degree of severity of the paresis. The largest amount of creatine, in excess of 1,000 mg. per 24 hours, was excreted in two patients (Cases 15 and 18) with only inconsiderable muscular weakness. In both these cases the condition appeared clinically to be relatively toxic, but the symptoms of the disease had been of only brief duration.

Our investigation has shown that electromyographic signs of myopathy occur even in patients with only slight muscular weakness. There is therefore reason to assume that the muscular weakness in almost all cases of thyrotoxicosis, and often interpreted as asthenia, is caused by a true myopathy. It is probably only a question of difference in degree between thyrotoxicosis with only slight muscular weakness and the disabling forms, so-called chronic thyrotoxic myopathy.

The electromyographical picture of myopathies was first described by Kugelberg (1947, 1949). He showed that the typical sign of proximal and distal muscular dystrophies, myotonic dystrophy, and myasthenia gravis was the occurrence of spike potentials with an abnormally short duration and a significant increase of polycyclic action potentials, the duration of which was mostly below that for the normal action potential. These findings have been confirmed by Walton (1952) by audiofrequency analysis. The same picture was observed in cases of dermatomyositis by Lambert, Beckett, Chen, and Eaton (1950), by Guy, Lefebvre, Lerique, and Scherrer (1950), and by Buchthal and Pinelli (1953), and in thyrotoxic myopathy by Sanderson and Adey (1952). Millikan and Haines (1953) reported on nine patients with chronic thyrotoxic myopathy. An E.M.G., performed in three cases, was normal.

In the present investigation the E.M.G. was abnormal in all the 17 cases examined. The pattern was quite characteristic of myopathy with patchily distributed small areas of abnormal potentials—rapid diphasic and polyphasic potentials lasting up to 6 milliseconds. The number of abnormal areas varied according to the degree of paresis—a greater number of such spots was observed in markedly weak than in slightly paretic muscles. No statistical analysis of the mean duration of the potentials was made since these abnormal potentials were not uniformly distributed. This may also be the case in progressive muscular dystrophy, according to Kugelberg (1953), where " the pathological changes often have a patchy distribution and vary with the severity of the disease ". He adds further: " The difficulty of obtaining statistically valid values of mean durations of potentials is well understood."

Fibrillation potentials, a common sign in lesions of peripheral neurones, was observed by Kugelberg and Petersén (1949) in cases of hereditary distal myopathy. This sign of increased excitability has also been found in myositis by Lambert *et al.* and by Guy *et al.* In the present cases fibrillations have only been observed in two patients (Cases 5 and 7): in one patient (Case 7) such potentials were led off both from those muscles showing signs of peripheral neuropathy and from the quadriceps muscles, the electromyographic picture of which was typical of myopathy. The electrographic pattern of the quadriceps muscles in the other patient (Case 5) was somewhat difficult to interpret; it was not quite clear if it was due to a lesion of the peripheral motor neurones or to myopathic changes. As all the other clinical signs pointed to thyrotoxicosis, so the aetiology, " primary " myositis, could be discarded in both these cases.

As a rule, the histological changes in the musculature were slight, and in the majority of patients no definite pathological changes were observed other than a certain degree of atrophy of the muscle fibres. This would seem to agree on the whole with the reports in the literature with the exception of Askanazy's study (1898), which is based on necropsy material. The change that appears to be the most constant according to the literature, namely adipose infiltration in the muscles, was not observed in our material. In only two cases were relatively pronounced histological changes with necroses in the musculature recorded. The semilunar accumulations of metachromatic substance inside the sarcolemma described by Asboe-Hansen, Iversen, and Wichmann (1953) were not encountered in the two patients examined for them.

Summary

In 20 cases of thyrotoxicosis systematic studies of the musculature, including electromyography and muscle biopsy, were performed in addition to the usual clinical examinations. Of these 20 patients, 10, seven women and three men, were severely disabled by pronounced muscular weakness. The other 10 patients had only slight to moderate muscular weakness.

Clinical signs of thyrotoxicosis in the 10 cases presenting high-grade muscular weakness were only slightly pronounced; thyrotoxic eye symptoms were

completely absent. In consequence many of these cases had remained untreated for many years.

In a number of cases the muscular weakness began several years before definite clinical signs of thyrotoxicosis were observed. In all cases but one the weakness was principally localized to the proximal muscle groups and then primarily to the lower extremities.

Five of the 10 patients with crippling muscular weakness had impaired carbohydrate metabolism of diabetogenous type. Pathological spontaneous creatinuria occurred in all of these 10 cases. No correlation was demonstrated between the degree of muscular weakness and the creatinuria.

Electromyographic examination showed signs of myopathy in the 17 cases in which the quadriceps or deltoid muscles were examined. There is therefore reason to assume that the muscular weakness in almost all cases of thyrotoxicosis and interpreted as asthenia is caused by true myopathy. Probably there is only a difference in degree between thyrotoxicosis with only slight muscular weakness and the disabling forms, so-called chronic thyrotoxic myopathy.

The histological changes in the musculature were slight as a rule. No pathological increase in adipose tissue in the musculature was observed. In only two cases were relatively pronounced histological changes with necrosis in the musculature recorded.

In one case both neuropathy and myopathy were demonstrated electromyographically. Histologically, signs indicating myopathy and degenerative changes in single nerves were observed.

Our material indicates that thyrotoxicosis untreated for a long period is probably one of the principal factors in the origin of disabling thyrotoxic myopathy.

Our thanks are due to Professor Eric Kugelberg for much valuable criticism of the electromyographic part of this work.

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INDIVIDUAL VARIATION IN THE SIZE OF THE TENTORIAL OPENING

BY

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Pathological study of transtentorial herniation in man is made difficult by the fact that manipulation of the unfixed brain within the skull quickly leads to distortion. Moreover, when the brain is removed in the conventional way by approaching it from above, both its blood vessels and the dural sheath are eventually cut through at the very level that ought ideally to be preserved.

If it were practicable, therefore, a more revealing approach might well be that directed through the base of the skull, the brain having been fixed *in situ*. In this way the tent would be completely exposed from below and its relation to the brain-stem and surrounding structures could be more precisely examined since they would remain intact.

In order to do this, however, a simple technique is needed which would not only make it possible to obtain such a specimen during a routine post-mortem examination but would also allow for complete and immediate artificial reconstruction of the head.

Remarkably enough, although Martin (1952) and Small and Woolf (1957) both refer to the removal of the skull in special cases, no such technique for general use appears to be described, and it is for this reason that the present method is reported.

It has been carried out so far in 21 cases, which were collected at random but mostly from mental hospital patients in order to illustrate the anatomical relationships of the temporal lobes and their blood supply to the brain-stem and the tentorial edge.

In the course of this study, an unexpected finding has been the marked variation from case to case in the size of the tentorial opening. This has been sufficiently striking to suggest that it might play a material part in the particular way that a given brain tends to herniate.

The present report therefore describes first a post-mortem technique for the study of the tentorium from below, and secondly the individual variation in the size and shape of the tentorial opening that has been revealed by the use of this method.

Post-mortem Technique

The soft tissues in the mouth and neck are removed in the usual way from below through a U-shaped incision, the arms of which, however, are continued up behind the ears to meet over the vertex. The two skin flaps are dissected off the skull. The anterior one is carried forward to the brows and, after a deep cut (on both sides) through the external auditory meatus, continued down past the lateral edge of the orbit as far as the angle of the jaw. The posterior flap is reflected back to high cervical level. A horizontal saw-cut is started anteriorly as if the whole skull cap were to be removed but it is carried back on both sides only as far as the coronal suture. A long, thin knife is passed between the temporal muscle and the zygomatic arch, and allowed to make its own way deep to the mandible into the neck. The line of the blade as it lies in the crook of the frontal process of the zygomatic bone is marked on the skull. The knife is withdrawn and the manoeuvre repeated on the other side. A coronal saw cut is then completed across the vault and along the line made by joining up these two marks. This cut will cross the ends of the horizontal one made earlier and so release a crescent of frontal bone which can be lifted out to reveal the dura overlying the pre-frontal areas. The membrane is snipped through and a "pre-frontal lobectomy" is completed by slicing off the exposed brain. The plane of this cut is a coronal one and usually passes just rostral to the tip of the anterior horns of the lateral ventricles.

A keyhole saw with a blade about 10 in. long is now passed on either side along the track left by the long knife, again ensuring both that the blade lies deep to the ramus of the mandible and that the point is clear of the skin flap in the neck. A saw cut is made coronally across the skull to the mid-line, and this is joined by a similar one which is made from the opposite side. The saw is withdrawn and once more inserted on each side in turn but with the teeth pointing posterolaterally in order to sever the temporo-mandibular joints. Any remaining soft tissue is cut through, and the face mask is lifted away.

The plane of the coronal saw cut lies at the back of the orbits but in front of the tip of the middle fossa so that the brain caudal to this remains intact.

Finally, a transverse saw cut is made through the vertebral column just below the foramen magnum. The skull block is now free (Fig. 1).

FIG. 1

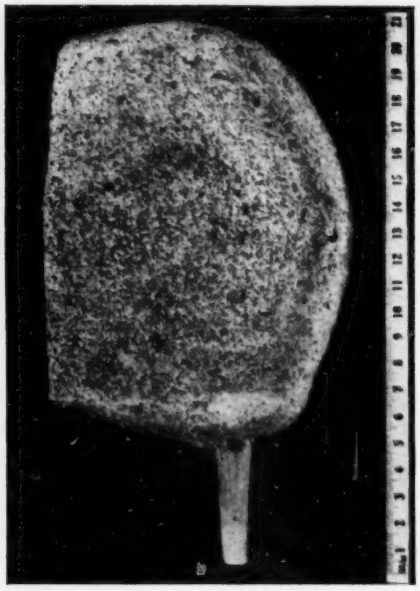

FIG. 2

FIG. 1.—Lateral view of the skull block after its removal from the body. × ½.

FIG. 2.—Lateral view of the cast used for replacement. × ½.

The head is immediately reconstructed by the insertion of a cast, kept in stock in two sizes, and pre-fabricated as follows. A wooden mould made in two halves is hollowed out to the required shape (that of Fig. 2). Its walls are greased with soft soap and it is packed with a mixture by weight of sawdust 4 parts, commercial plaster of Paris 6 parts, and water. This is a convenient mixture to use for casting since after a few hours' setting it is light and can be worked easily with a saw. A tapered wooden peg, which is destined to slide into the exposed vertebral canal, is embedded in the base at the time of mixing (Fig. 2). For use, the cast is slipped into position and the face mask laid on its flat surface. If necessary the edges of the cast are shaped with a saw to fit between the rami of the mandible. The crescent of frontal bone is replaced over a small pad of tow and the skin sewn up in the usual way.

With a little practice, this is a quick, simple and reliable technique, lengthening the post-mortem examination by about a quarter of an hour. The only extra instrument required is a carpenter's keyhole saw handle and a small stock of blades. An electrically-driven Desoutter necropsy saw, however, is an invaluable aid, especially for the further opening of the skull after fixation.

Fixation.—Before immersing in 10% formol saline, the anterior horns of the ventricles were opened. In the present series the fixing fluid was changed after one day, three days, and one week, and fixation was usually helped by partially opening the base and/or the skull cap either during the post-mortem examination or a few days after immersion.

It may be suggested that the appearance of the tentorial opening, investigated after death and after fixation, does not accurately reflect that present during life. Such a view cannot be absolutely refuted but it, nevertheless, seems untenable, for examination of the dural tent with its attachment to the base of the skull intact conclusively demonstrates its remarkable strength and rigidity as well as its smooth and regular outlines. However important are the effects of post-mortem change or of fixing fluid on the brain, it seems impossible that these could materially deform the free dura and thus the shape of the tentorial opening, without some distortion being readily identified. This was never found.

Opening of the Skull

The tentorial opening was approached from below by removing the floor of the posterior fossa in order to expose the brain-stem and cerebellum. A transverse cut through the pons made it possible to shell these structures out in one piece only, leaving behind the most dorsal part of the vermis and of the lateral lobes of the cerebellum. The edge of the tent was next defined and further progressively more rostral cuts made through the brain-stem until this level was reached. In some cases the remainder of the skull was then removed, the hemispheres being kept intact within their dural sheath (apart from the original pre-frontal ablation); in others only the cap was removed and the base of the skull was left with the dura still attached. In either case it was possible, by making appropriate cuts round the dura of the convexity and through the perforating vessels, etc., to lift out the brain in such a way that it could be replaced at will, much as an egg can be slipped into an egg cup.

The tentorium cerebelli with the brain in place was then photographed from below; the tentorium was lifted away and a second photograph was taken of the exposed base of the brain. In this way the exact relation of the dural edge to the adjacent cerebral structures was shown. A scale was included in each photograph and all enlargements were made to the same magnification.

Observations on the Tentorial Opening

In the following illustrations (Figs. 3 to 8) the pictures are the natural size. The right side of the

FIG. 3.—Case 12, female, age 33, the tentorial opening seen from below with the cerebral hemispheres and upper brain-stem in position. × 1.

FIG. 4.—Case 9, male, aged 65. × 1.

FIG. 5.—Case 6, female, age 65. × 1.

FIG. 6 —Case 5, female, age 51. × 1.

FIG. 7.—Case 1, male, age 53. × 1.

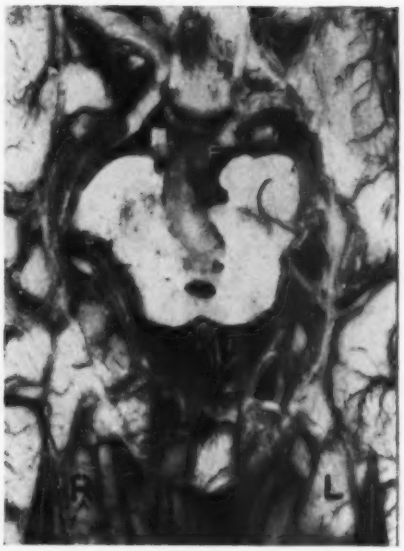

FIG. 8.—Case 7, male, age 83, the same view as previously but with the tent removed to show that its limits are still clearly marked out by the cut edge of the leptomeninges. × 1.

FIG. 9

FIG. 10

FIGS. 9 and 10.—Composite tracings of the male (Fig. 9) and female (Fig. 10) outlines. × 1.

brain is always on the left side of the photograph. Each illustration has the appropriate case number against it and can be identified in the first column of the table.

On comparing the series of photographs, it became obvious that the tent fitted round the brain-stem much more tightly in some cases than in others. At one extreme (Figs. 3 and 5) a major part of both hippocampal gyri would be exposed, while at the other virtually nothing was to be seen (Figs. 4 and 6). In some cases (Figs. 7 and 8) the two hippocampal gyri were unequally exposed.

The crucial difference did not lie either in the variation of the cross-sectional area of the brain-stem or even in the presence of brain swelling; it clearly lay in the size of the tentorial opening.

As the illustrations would suggest, the differences were sufficiently gross for a series to be roughly graded by eye, but since the photographic recording had been done systematically it was possible to

TABLE

CLINICAL DATA AND MEASUREMENTS OF TENTORIAL OPENING

Case No.	Sex	Age at Death	Cause of Death	Due to or in a Case of	Approximate Size of Tentorial Opening (sq. cm.)
13	F	69	Cerebral haemorrhage	Ruptured aneurysm	10
5	F	51	Cardiac infarction	Arteriosclerotic psychosis	10
11	M	65	Bronchopneumonia	Cryptogenic epilepsy	10
9	M	65	Carcinoma of bladder	—	10
21	F	79	Aortic stenosis	Paraphrenia	11
16	M	82	Carcinoma of oesophagus	Schizophrenia	11
18	M	88	Pulmonary embolus, femoral thrombosis	—	11
20	F	86	Bronchopneumonia	Cryptogenic epilepsy	11
14	F	40	Cerebral tumour	—	12
3	F	68	Cerebral haemorrhage	Arteriosclerotic psychosis	12
10	M	81	Cardiac infarction	Mania	12
19	F	93	Bronchopneumonia	—	13
17	F	79	Bronchopneumonia	Senile psychosis	14
15	F	69	Myocardial degeneration	Senile psychosis	14
8	F	66	Bronchopneumonia	Alzheimer's disease	14
2	M	74	Acute bronchitis	Depression	15
7	M	83	Cardiac infarction	Arteriosclerotic psychosis	16
6	F	65	Myocardial degeneration	Cryptogenic epilepsy	16
4	M	79	Aortic stenosis	Mania	17
1	M	53	Wernicke's encephalopathy	Pulmonary tuberculosis	18
12	F	33	Haemorrhagic leuco-encephalitis	—	23

demonstrate the range a little more clearly, first by estimating the approximate size of the area in each case, and secondly by building up composite tracings of the individual outlines.

It must be emphasized that both the measurements and the tracings are intended as rough guides and relate only to the present series in which a particular technique was used. They record, not the real size and shape of the opening, but that found when the dorsal curvature of the tent has been flattened out and so foreshortened. In the present context greater accuracy would seem to be unnecessary. It might even be misleading, since the outline of the tent itself, especially along its anterior border, is not always clear cut.

The measurements are tabulated with details of each case and arranged simply in order of the size of the tentorial opening.

For the tracings, the cases were first split into male and female; the magnification is the same as that in the previous illustrations, namely × 1.

Nine males and 12 females were examined, the age at death ranging from 33 to 93, but with two-thirds over 65.

The size of the tentorial opening in these cases therefore ranged from about 10 to about 23 sq. cm.; that is, the largest was over twice the size of the smallest. The tracings explain themselves.

Discussion

It is conceivable that these differences might be related to sex or to the atrophy of old age but the distribution of the cases in the table gives little or no support to either suggestion. At the same time, it is difficult to imagine what other factors might be of importance for—short of tearing—the tentorium seems too strong and too well anchored to be stretched once its development is complete.

In other words, the outline of the opening presumably remains virtually constant during adult life and is established during the period of growth. Its variability then from case to case is simply a manifestation of the range of normal development, although the possible influence of pathological conditions occurring in early life should not be ignored.

From the applied point of view, however, the salient fact is that such marked variation occurs at all for the pattern of any herniation must be to some extent affected by the size and shape of the ring through which the brain is being forced.

Although it is not possible to go further than this at present, such an assertion could easily be tested by applying the same technique to an adequate series of cases with raised intracranial pressure. In relation to the problem of herniation in general, it might also be useful to compare diagnostic injection studies, either of the ventricles or of the blood vessels, carried out during life with these repeated after death.

Such an approach, in fact, might well provide fresh information about a number of those conditions in which the brain is thought to have moved decisively within the skull. It was for the study of one of these—the relation of the infero-medial parts of the temporal lobe to epilepsy—that the present technique was originally planned, and is now being used.

Summary

A post-mortem technique is described for the routine removal of the brain, apart from the prefrontal areas, within the skull.

Using this method, the tentorial opening has been studied in 21 cases and a marked individual variation in its size is described.

The possible implications of this to transtentorial herniation are briefly discussed and other ways in which the technique might be of use are suggested.

I am very grateful to Dr. R. Ström-Olsen for his encouragement in carrying out this work and to Dr. D. C. Caldwell and Dr. W. H. Bennison for their cooperation in the collection of material.

I would particularly like to thank Professor Peter Daniel, Dr. J. B. Brierley, and Dr. Sabina Strich for their active help and advice at all times.

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ARTERIES OF THE SPINAL CORD IN THE CAT*

BY

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The purpose of this paper is to describe the pattern of arteries supplying the spinal cord in the cat and to present the results of experimental occlusion of certain tributaries of the ventral spinal artery.

Despite the extensive use of the cat in neurological research, surprisingly little has been written about the circulation through the spinal cord in this animal and the original description by Tauber and Langworthy (1935) made no mention of the relative size or importance of the various segmental anastomoses. Subsequent studies in man by Suh and Alexander (1939), in the monkey by Yoss (1950), and in the rat by Woollam and Millen (1955) have shown that there is a considerable disparity in the size of tributaries of the ventral spinal artery. Thus, in man, there are only six or eight unpaired ventral lateral spinal arteries which are greater than 250μ in diameter. These are the only vessels which are likely to make any significant contribution to blood flow within the ventral spinal artery. Papers, published in abstract form, by Groat (1945) and Brightman (1956) do not indicate whether these features also obtain in the cat. Furthermore, their technique entailed perfusion of a mixture of formalin, Indian ink, gelatin, and saline into the aorta of the cat and we have found this method unsatisfactory, for the site of injection is too far removed from the vessels of the spinal cord and the uneven consistency of the injection mass does not permit filling of the smaller arteries. Both disadvantages are avoided in the present study.

The second section of this paper is concerned with occlusion of certain segmental tributaries of the ventral spinal artery. Interest has been focused in recent years on the possible rôle of ischaemia in the production of lesions of the spinal cord and in particular on the myelopathy associated with cervical spondylosis. Mair and Druckman (1953) described the pathology of two patients with cervical spondylosis and a case of myelopathy which came to necropsy. They concluded that the location of the spinal cord lesions favoured insufficiency of the ventral spinal artery as the underlying cause. In 1957, I made a survey of 32 patients with osteoarthritis of the cervical spine who were submitted to cervical laminectomy and found no evidence to support the contention that osteophytic ridges had caused pressure either upon the ventral spinal artery or upon the spinal cord (Bradshaw, 1957). However, owing to the limits of the operative field, it was impossible to exclude compression of the radicular arteries, which are tributaries of the ventral spinal artery, within the intervertebral foramina either by osteophytes or fibrosis of the meningeal root sleeves. Suh and Alexander (1939) have shown that there are only two or three large segmental tributaries of the ventral spinal artery in the cervical region, and the development of a myelopathy in patients with cervical spondylosis might depend on whether one of these critical arteries had been compressed. Indeed, the lack of correlation between the osteophytic ridges as shown by myelography and the level of the clinical neurological deficit suggests that the cause of the myelopathy is not uncomplicated cord compression.

It seemed important, therefore, to determine by animal experiment whether it is possible to provoke an ischaemic myelopathy by occluding one of the larger ventral lateral spinal arteries or its parent vessel, the radicular artery.

A preliminary study was made of the spinal circulation of the gibbon and rhesus monkeys and of the dog. Though, in these animals, there was a considerable disparity in the size of the ventral lateral spinal arteries and asymmetry of their distribution, there was also a marked individual variation in the levels at which the larger segmental anastomoses occurred. This variation made it impossible to occlude a large radicular artery by a selective operation.

The present study of the pattern of spinal arteries in the cat showed that though the segmental tribu-

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taries of the ventral spinal artery in the cervical region were approximately equal in size, this pattern did not obtain in the thoracic and lumbar regions. A very large ventral lateral spinal artery regularly accompanied the fourth lumbar nerve root on the left side and, for this reason the radicular arteries between L.2 and L.6 were occluded in the cat.

Material and Methods

Injection of Spinal Arteries with Latex Solution.—The thorax was opened under nembutal anaesthesia in eight cats, the pericardium incised, and a plastic cannula introduced into the left cardiac ventricle. The cannula was secured in position with artery forceps and the right auricular appendage was slit open. Exsanguination was carried out by the perfusion of 500 ml. normal saline through the cannula from a gravity bottle at a height of three feet. When this had been done, the cannula was reconnected to a pressure bottle containing 400 ml. of 10% formaldehyde (unneutralized) and this was perfused at a pressure of 150 mm. Hg.

Major arteries within the thorax were identified and exposed by blunt dissection and three ligatures were tied as follows: the first around the ascending arch of the aorta and the second and third around the beginnings of the innominate and subclavian arteries respectively. Distal to each ligature a short length of polyethylene tubing was introduced into the arterial lumen and tied in position. Care was taken to avoid pushing the tubing beyond the left common carotid branch of the innominate artery, the vertebral branch of the left subclavian artery, and the first intercostal branch of the aorta respectively.

Latex solution becomes sticky in contact with glass and solidifies in an acid medium and therefore it is necessary to use an all-metal syringe, previously washed clean of formalin. The syringe was connected in turn to each of the three lengths of polyethylene tubing and the following amounts of latex injected: aorta, 25 to 35 ml., innominate, 7 to 12 ml., left subclavian 5 to 10 ml. Pressures applied to the plunger of the syringe were not measured; usually sufficient latex had been injected into the aorta when filling of small arteries over the bladder wall became visible.

The extradural course of the relevant arteries was studied by dissection, and the brain, spinal cord, and proximal portions of nerve roots, together with their meningeal coverings, were removed in the usual manner. The pattern of the spinal arteries was determined and the diameters of the injected vessels measured under a dissecting microscope.

In four animals the above procedure was modified as follows. After perfusion with formaldehyde a laminectomy, limited to two adjacent vertebrae, was done and a single pair of nerve roots exposed extradurally within the spinal canal. A ligature was tied tightly about one pair of nerve roots to occlude the radicular arteries. Latex was then injected as before.

Injection of Spinal Arteries with Vinyl-lead-acetone.—Techniques for the preparation, injection, and subsequent radiography of vinyl-lead-acetone have been described by Kaplan (1953, 1956). In the present study three cats were used and the initial procedures for exsanguination and formaldehyde perfusion have already been described.

The injection mass was prepared by shaking 6 g. of vinylite powder in 60 ml. of acetone until a solution had been made. Two parts of this mixture were then added to three parts of a liquid lead compound, known as " 126 " (National Lead Company, Brooklyn), while the latter was thinned by heat on a water-bath. The surface precipitate that formed was discarded and a part of the remainder was injected through a fine metal cannula into the vertebral arteries. It was necessary to apply considerable force to the plunger of the syringe to fill the small intrinsic vessels of the spinal cord from the vertebral arteries and, as the solution solidifies rapidly, the whole procedure had to be completed within a few minutes. The spinal cord was removed and radiographed using a 3 mm. focal spot, a 50 Kv., 10 M.A. *x*-ray tube, and an exposure time of one second. In addition, radiographs were taken of transverse slices of spinal cord 1 to 3 mm. in thickness, using a 0·5 mm. focal spot, 1 Kv., 45 M.A. *x*-ray tube, and an exposure time of $\frac{1}{2}$ second. Type " M " industrial film and cardboard cassettes were employed and the negatives were enlarged and printed on high-contrast paper.

Division of Pairs of Radicular Arteries in Live Animals.—Seventeen adult female cats were used. Under nembutal anaesthesia and with an aseptic technique, a longitudinal skin incision was made over the spines of the appropriate vertebrae, the deep fascia incised, and the posterior spinal muscles scraped of their bony attachments. The spinous processes and central portion of two adjacent laminae were removed. Epidural fat was teased away with blunt forceps in order to minimize venous haemorrhage before extending the laminectomy to its full lateral extent. The appropriate pair of lumbar nerve roots was identified and divided extradurally within the spinal canal. Any resultant bleeding was controlled by the temporary application of cotton strips between the dura and the wall of the bony canal. The deep fascia and skin were closed in two layers and the wound sealed with a collodian dressing. Intramuscular penicillin, 300,000 units daily, was given for the first two post-operative days.

The single pairs of lumbar nerve roots divided were as follows:

Number of Animals	Pair of Nerve Roots Divided
2	L.2
3	L.3
4	L.4
4	L.5
2	L.6

In two other cats the fourth pair of lumbar nerve roots was exposed but left intact to serve as controls.

Animals were examined daily after operation for evidence of cutaneous sensory loss to pin prick, retention of urine, the placing responses of the hind limbs, the deep tendon reflexes, the pinch reflexes, and gait. Twelve animals were sacrificed by exsanguination and perfusion with 10% formalin under nembutal anaesthesia on the 14th post-operative day; of the remainder, four (that contracted distemper) on the eighth, and one (with a

wound infection) on the ninth post-operative days. The whole spinal cord was removed within an hour of death, the presence of the lesion was confirmed, and the spinal canal inspected to exclude vertebral subluxation, disc herniation, infection, and haematoma formation. Sections of the spinal cord were examined macroscopically before they were embedded in paraffin or celloidin. Serial sections were taken from the segment of cord adjacent to the root section and two out of every 10 were stained alternatively with Nissl and Mahon's stains. Four sections were cut from each of the two segments rostral and caudal to the root section and stained with Marchi and Mahon's methods; four other sections were taken from both the mid-thoracic and the lower cervical regions and stained with Mahon's stain. All sections were 20μ thick.

Results

Extrinsic Arteries of Spinal Cord.—The vertebral arteries arose from the first part of the subclavian arch at approximately the same level on either side, ascended to the transverse processes of the sixth cervical vertebra, traversed the vertebral foramina, and, adjacent to the ventral surface of the first cervical nerve roots, pierced the meningeal root sleeves to enter the subarachnoid space. After giving off meningeal branches to the posterior fossa, they continued in a rostral and medial direction to the lower border of the pons where they united to form the basilar artery. The subarachnoid portions of the vertebral arteries were 550 to 1,050μ in diameter. Opposite each intervertebral foramen, between C.2 and C.7, the vertebral arteries gave off lateral branches, the vasa nervorum and arteries to neighbouring muscle, and a medial branch which entered the intervertebral foramen as the radicular artery. Caudal to C.7 the radicular arteries were derived from the intercostal, lumbar, and sacral arteries. In all regions the radicular arteries divided into a dorsal and ventral branch which accompanied the sensory and motor roots respectively. These are the lateral spinal arteries.

The ventral lateral spinal arteries provided branches to the ventral spinal dura and the vertebral bodies and continued in a rostral and medial (sometimes a caudal and medial) direction as tributaries of the ventral spinal artery. Their junction with that vessel was either direct or via a number of short branches. Not all of the ventral lateral spinal arteries were of the same size. In the cervical region (Figs. 1 and 2), between C.3 and C.8 their diameters were approximately equal, with occasional exceptions, and measured 120 to 280μ. At C.2 the arteries were small, 10 to 40μ. In the thoracic and lumbar regions (Fig. 3) there was considerable variation between individual specimens and asymmetry of arrangement. There were only eight to

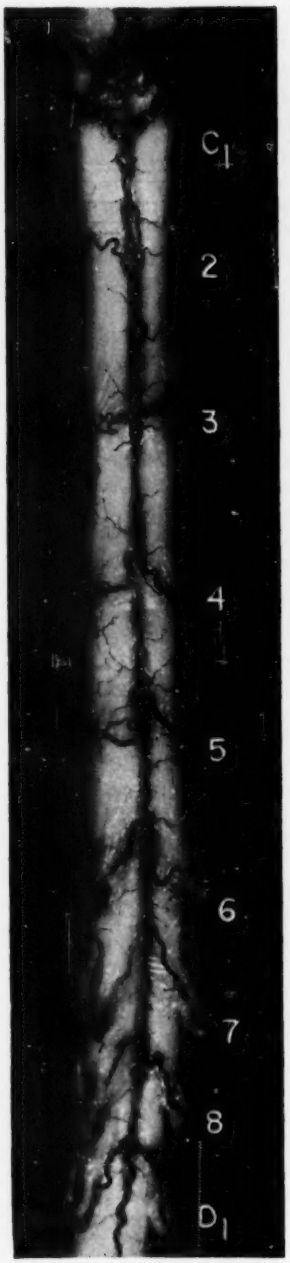


FIG. 1.—Ventral aspect of cervical cord injected with latex. Instead of a ventral spinal artery there are several small parallel vessels. The rostral limit, formed by descending branches from the vertebral arteries, can be seen. The ventral lateral spinal arteries are small at C.2 on both sides and at C.3 on the right.

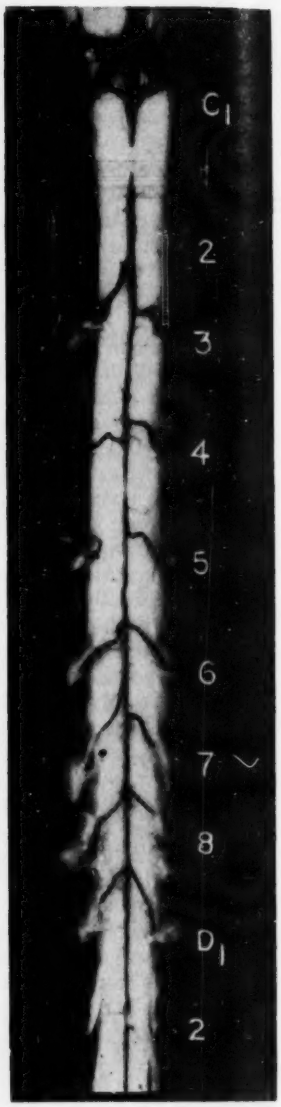


FIG. 2.—Ventral aspect of cervical cord injected with latex. The ventral spinal artery is narrowest at C.2 and the symmetry of the segmental tributaries can be seen.

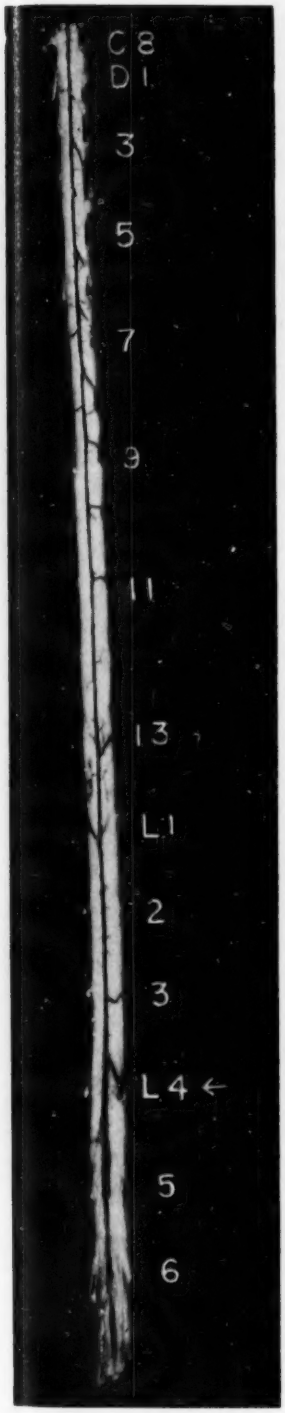


FIG. 3.—Ventral aspect of thoracic and lumbar cord injected with latex, showing the asymmetry of the segmental arteries. Most of the large ventral lateral spinal arteries are on the left ; a very large one is visible at L.4.

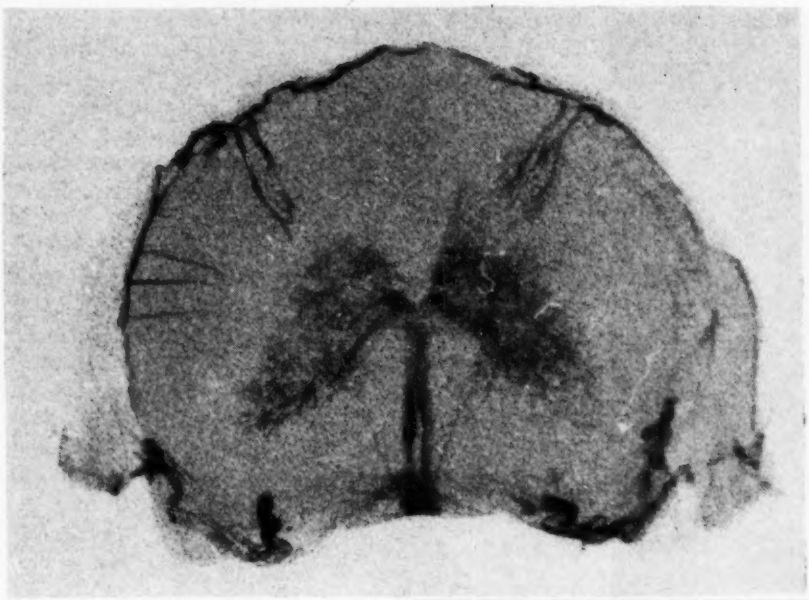
FIG. 4.—Dorso-lateral aspect of thoracic cord injected with latex. One of each pair of the medial and lateral dorsal spinal arteries can be seen on the right.

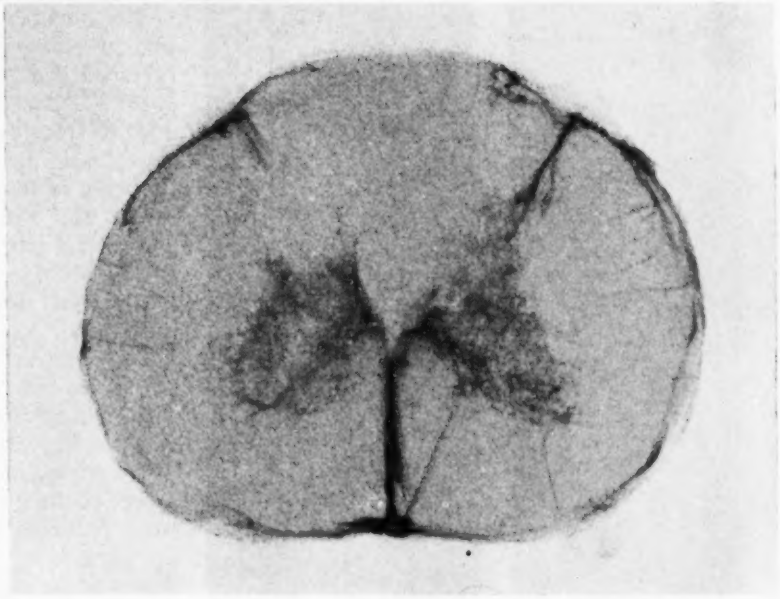
14 unpaired ventral lateral spinal arteries in the thoracic and three to five in the lumbar region which were greater than 100μ in diameter; the remainder were very small, 30 to 60μ. Furthermore, the majority of the larger vessels were located on one side, usually the left. A feature constant to all specimens examined was a large artery, 250 to 300μ in diameter, at L.4 on the left side.

The dorsal lateral spinal arteries gave off branches to the dorso-lateral spinal dura and continued on the ventral surface of the sensory nerve roots as far as the dorsal root entry zone and there divided into ascending and descending branches which anastomosed to form the lateral pair of dorsal spinal arteries (Fig. 4). Diameters of the dorsal lateral spinal arteries were 25 to 150μ (average 60μ) and there was a considerable variation in the distribution of the larger vessels in different specimens. In general, the larger ones were found in segments where the ventral lateral spinal artery was small, for example, at C.2.

The dorsal spinal arteries were small in calibre and in no single specimen was adequate injection obtained throughout the whole length of the spinal cord. Caudal to C.5-7, there were four dorsal spinal arteries (Fig. 4), namely, a lateral pair, formed by the anastomosis of ascending and descending branches of the dorsal lateral spinal arteries, and a medial pair which arose as branches of the former. The lateral pair were 50 to 100μ diameter and lay at the level of the dorsal root entry zone often covered by the most dorsal fibres of the sensory roots; the medial pair were 25 to 50μ in diameter and lay in the dorsolateral fissures. Between C.5 and C.7 each of the medial pair of dorsal spinal arteries was seldom a continuous structure and was represented by branches which arose from the lateral pair and which passed in an irregular fashion over the dorsal aspect of the spinal cord. Rostral to C.2, numerous small branches from the vertebral arteries encircled the cord from its ventral aspect and supplied the region of the dorsal columns. From each of the four dorsal spinal arteries and from the ventral spinal artery there were circumferential branches which formed a continuous arterial ring around the spinal cord, and from the lateral pair of dorsal spinal arteries there arose branches which penetrated into the substance of the dorsal horns.

The ventral spinal artery extended from the level of the foramen magnum to the conus medullaris and lay superficially in the ventromedian sulcus though, occasionally, for a few segments, it dipped deeper into that space. In some specimens it was represented by several small and parallel vessels. The rostral limit was formed by the junction of several descending branches of the vertebral arteries,





FIGS. 5 and 6.—Enlarged radiographs of slices of cervical cord injected with vinyl-lead-acetone. The bilateral distribution of a median sulcal branch to supply the spinal grey matter can be seen, together with some of the circumferential and penetrating branches.

whereas its caudal extent was continuous with the lower sacral arteries. The largest diameters were 300 to 425μ in the regions of the spinal enlargements and the smallest were 100 to 185μ in the thoracic region and at the level of the second cervical segment. Throughout its course it was reinforced by segmental tributaries, the ventral lateral spinal arteries. Between each pair of these tributaries there were three to nine circumferential branches which were asymmetrically arranged and passed around the ventro-lateral surface of the spinal cord to anastomose with those from the dorsal spinal arteries. Other branches of the ventral spinal artery passed into the ventro-median sulcus.

Intrinsic Arteries of the Spinal Cord.—There were two to four unpaired branches of the ventral spinal artery in each spinal segment which entered the ventro-median sulcus and pierced the white spinal commissure. At levels slightly ventral to the central canal, or on either side of it, these median branches divided into a fine arterial network which was distributed throughout the ventral and lateral grey matter (Figs. 5 and 6). Larger branches entered the base of the dorsal horns where they anastomosed with penetrating branches from the lateral pair of dorsal spinal arteries; this intramedullary anastomosis occurred from one to three times in each cervical segment. The white matter, by contrast, had a much poorer blood supply from small penetrating branches which arose from the circumferential anastomotic ring. Such vessels were small in diameter and it is probable that many failed to fill with the injection mass, but they seemed to be most numerous in the region of the lateral columns.

Occlusion of Radicular Arteries before Injection of Latex.—The symmetrical arrangement in the cervical region of the tributaries of the ventral spinal

artery suggested that blood flow within that artery would not be materially lessened by ligation of any single pair of radicular arteries, with the possible exception of that at C.3. It will be recalled that there is no large ventral lateral spinal artery at C.2 so that ligature of the segmental anastomoses at C.3 might impair circulation in the rostral part of the cervical cord. However, ligation of the single separate pairs of radicular arteries at C.3, C.4, and C.6 and, in the lumbar region, of L.4, did not lead to a filling defect in the ventral spinal artery when latex solution was subsequently injected.

Division of Pairs of Lumbar Radicular Arteries in the Live Cat.—Following the division of single pairs of lumbar nerve roots, together with the radicular arteries that accompanied them, most of the 17 animals subjected to these operations exhibited a neurological deficit. The placing responses were impaired or lost in 12, and in nine of these the state of the deep tendon reflexes in the hind limbs was also abnormal by reason of inequality, exaggeration, or loss. In addition, these cats walked with their hind limbs in a position of partial flexion and were unsteady on their feet. None of these abnormalities persisted for more than four or five days and the severity and duration of the disturbances were unrelated to the level of the root section. Since these phenomena also occurred in the two controls, in which a pair of nerve roots had been exposed but left intact, it is probable that they were caused by operative trauma to the spinal cord rather than by occlusion of the radicular arteries. When these abnormalities had disappeared, it was possible to detect weakness, limited to muscles innervated by those nerve roots which had been sectioned. At the end of seven to 10 days the disability had become minimal and did not limit activity.

Histological examination of the spinal cords failed to reveal any signs of ischaemic myelopathy. Certain minor changes which were seen included a reduction in the number of ventral horn cells at the level of the lesion and areas of partial demyelination around the circumference of the spinal cord at the same level.

These results show that surgical division of single pairs of lumbar radicular arteries in the cat, including the parent vessel of the large ventral lateral spinal artery at L.4 on the left, does not cause an ischaemic myelopathy. In the cat, at least, blood flow within the ventral spinal artery is sufficient to maintain normal structure and function of the spinal cord when a single pair of its segmental tributaries is occluded.

Summary and Conclusions

The extrinsic arteries of the spinal cord have been studied in the cat after the injection of latex into the left subclavian and innominate arteries and the thoracic aorta. Though the general arterial pattern resembles that which has been reported for man there are important differences.

(1) Segmental tributaries of the ventral spinal artery in the cat are approximately equal in size between C.3 and C.8; in man there are two or three large unpaired tributaries and the remainder are small.

(2) In the thoracic and lumbar regions these segmental tributaries are unequal in size and the larger vessels are situated predominantly on one side in both the cat and man, but large tributaries are more numerous in the cat.

(3) There is a large ventral lateral spinal artery on the left side at L.4 which was constantly present in all of the 10 cats examined.

(4) The spinal dura is more vascular in the cat than in man.

The intrinsic arteries of the spinal cord have been studied in the cat by radiology after the injection of vinyl-lead-acetone into the vertebral arteries. Features which distinguish the pattern of spinal arteries in the cat from that reported for man include the following:

(1) Median branches of the ventral spinal artery, which enter the ventro-median sulcus and pierce the white spinal commisure, each supply the grey matter on both sides whereas in man it is reported that each branch has a unilateral distribution.

(2) Within the dorsal horns there is an extensive anastomosis between the ventral and dorsal spinal arteries which has not been described in man.

The ligation of single pairs of radicular arteries in the cervical region and at L.4 in the cat does not prevent subsequent filling of the ventral spinal artery with latex. When single pairs of lumbar radicular arteries are severed in the living cat there are no permanent sequelae to suggest an ischaemic myelopathy and when these animals are sacrificed at 14 days the gross histology of the spinal cord is normal.

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ACCOMMODATION IN THE HOLMES-ADIE SYNDROME

BY

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In 1936, Bramwell suggested that the title "Holmes-Adie syndrome" be given to the clinical complex of a slowly reacting pupil and absent tendon reflexes in recognition of the descriptions by Holmes (1931) and Adie (1932). Both authors had emphasized the chief clinical features—dilatation of the pupil, apparent loss of the reaction to light, slow constriction and relaxation in response to near and distant vision, and partial loss of the tendon reflexes. Although the syndrome had been recognized wholly or in part many years previously (Strasburger, 1902; Saenger, 1902; Nonne, 1902; Markus, 1906; Weill and Reys, 1926), credit must go to Adie for stressing the benign nature of the disorder and distinguishing it clearly from neurosyphilis.

In addition to the various abnormalities of the pupil, disturbances of accommodation have been described in the Holmes-Adie syndrome; Kyrieleis (1951) stated that they occurred in more than 20% of cases and Graveson (1949) found them in 16 out of 22 affected eyes. Little attention has been paid to the mechanism of the abnormality of accommodation. This paper reports the investigation of disordered accommodation in 15 patients in whom the Holmes-Adie syndrome had been present for 14 months or longer. A comparison is made between the abnormality of accommodation and that of the pupil. In view of the intimate anatomical and physiological relationships between the iris and the ciliary muscle, it is reasonable to look for similar disturbances of function as a result of disease.

A short review of our knowledge of the pupillary abnormality in the Holmes-Adie syndrome will serve as a basis for comparison. The Holmes-Adie pupil has a definite evolution. There is often an early stage of internal ophthalmoplegia when the pupil is fixed to both light and convergence; after an interval of weeks or months there follows the later stage in which the typical Holmes-Adie pupil develops its tonic reaction (Rothmann, 1903; Axenfeld, 1919; Reitsch, 1925; Alajouanine and Morax, 1938). By the term "tonic reaction" is generally meant the slowness of pupillary constriction and the even slower pupillary dilatation in response to near and far vision respectively. But it has also been noted that the reaction to convergence may be remarkably wide in its range, considering that it often follows a stage of complete paralysis (Strasburger, 1902). Not only is the reaction to convergence well preserved when compared to the reaction to light, but it may in fact be excessive (Alajouanine and Morax, 1938; Heersema and Moersch, 1939). In assessing the degree of tonicity there are, therefore, two criteria: slowness of pupillary movement and preservation of the range of movement.

Adler and Scheie (1940) showed that the tonic pupil constricts after the conjunctival instillation of the weak parasympathomimetic drug acetyl-B-methylcholine, in concentrations which have no effect on normal pupils. Scheie (1940) accounted for the slow constriction during convergence of the eyes by a similar sensitivity of the sphincter pupillae to acetylcholine released by any surviving parasympathetic fibres. He explained the slowness of relaxation as the delay required for the destruction of acetylcholine by cholinesterase. This hypothesis of hypersensitivity of the partially denervated sphincter pupillae is in accordance with the law of denervation put forward by Cannon and Rosenblueth (1949) who stated that, when a chain of neurons is severed, there results after an interval a hypersensitivity of the distal elements and effectors to the action of nerve impulses, and to certain chemical agents either injected parenterally or applied locally.

A paralysis or weakness of accommodation often results as part of the internal ophthalmoplegia which may be the early stage of the syndrome. During the later stage, when the fixed pupil changes into a tonic one, there is an accompanying improvement in accommodation (Holmes, 1931; van Leeuwen, 1946). From the clinical standpoint, the early stage may be manifested by blurring of vision; the patient is unable to read small print with the affected eye owing to recession of the near point. During the later stage, the range of accommodation is restored, with improvement of vision, but there often remains a slight disability—accommodation may be delayed

before either the near or the distant object is seen clearly. As in the case of the slow pupillary constriction, slow accommodation has been termed tonic. Graveson (1949) reported tonic accommodation for near vision in the majority of his patients. However, other authors found that the greater delay in accommodation occurs for far vision (Markus, 1906; Reitsch, 1925; Holmes, 1931; Adie, 1932; Heersema and Moersch, 1939); the patient is unable to relax accommodation when looking from a close to a distant object. This symptom has been termed spasm of accommodation; it can also be induced in normal subjects by instilling powerful parasympathomimetic drugs into the conjunctival sac. It has already been mentioned that there is an increase in the sensitivity of the tonic pupil to the drug acetyl-B-methylcholine. These two facts suggest the possibility of an increased sensitivity of the ciliary muscle to parasympathomimetic drugs.

In the Holmes-Adie syndrome the defect of accommodation appears to follow the same sequence as that of the pupil: paralysis followed by a tonic reaction. It was considered worthwhile verifying this supposition and the following questions were therefore asked:—

(1) Is there a recovery in the range of accommodation by the time the tonic pupil has developed ?

(2) Is there a delay in accommodation ?

(3) Is the affected ciliary muscle more sensitive to parasympathomimetic drugs ?

Material

Accommodation was examined in 15 patients with the Holmes-Adie syndrome. Table I shows details of their age, sex, pupillary abnormalities, and tendon reflexes. In every patient the blood Wassermann reaction was negative; in six patients (Cases 2, 3, 4, 9, 13, and 15), on whom a lumbar puncture was performed, the Wassermann reaction in the cerebrospinal fluid was likewise negative. Among these patients 20 eyes were selected for examination, using two criteria: (*a*) Each eye had to show a well-established tonic pupil. The severity of the pupillary abnormality was judged by the abolition or severe impairment of the light reflex. (*b*) A sufficient interval of time had to elapse after the onset of the disorder (14 months or longer). This interval would permit the development of tonic accommodation if such a change were going to occur.

It was considered essential to compare the eyes of the Holmes-Adie patients with the eyes of normal subjects, and to match each patient with a normal subject for age and sex. It is well known that normal accommodation diminishes with age. Owing mainly to sclerotic changes in the crystalline lens, accommodation decreases from birth onwards, until it is lost around the age of 50 to 60; different ages are quoted for the total loss of accommodation, according to the authority and the method of measurement (Hamasaki, Ong, and Marg, 1956). Furthermore, for any given age, there is a physiological range of up to 4 dioptres for normal accommodation (Duane, 1925). A particular effort was made to obtain a close agreement in age; the age in years of the normal control agreed exactly with that of the patient in 11 cases, and within a year in four cases (Table II). Care was also taken not to include as a normal control any subject with a severe refractive error. Where the abnormality was bilateral, both eyes of the control were tested: where it was unilateral, only the corresponding eye was examined.

TABLE I

CLINICAL FINDINGS IN FIFTEEN PATIENTS WITH HOLMES-ADIE SYNDROME

Case	Age	Sex	History	Clinical Features	Tendon Reflexes
1	57	F	Blurred vision (1924)	Oval tonic left pupil	Absent T.J.s, K.J.s, and A.J.s
2	56	F	Incidental finding (1955). History of delayed accommodation	Bilateral irregular tonic pupils	All absent
3	53	M	Incidental finding (1955); glare	Oval tonic pupil, ptosis and facial anhidrosis on the left	A.J.s sluggish
4	49	M	Incidental finding (1955)	Irregular tonic pupil and slow accommodation on the right	Absent A.J.s
5	43	M	Sudden blurred and double vision (1956)	Bilateral irregular tonic pupils and slow accommodation	Normal
6	42	M	Delayed accommodation and unequal pupils (1951)	Bilateral irregular tonic pupils and slow accommodation	Absent A.J.s
7	38	F	Incidental finding (1956). Delayed accommodation	Bilateral irregular tonic pupils and slow accommodation	Absent B.J.s, T.J.s, K.J.s, and A.J.s
8	38	F	Incidental finding (1954)	Irregular tonic left pupil; normal accommodation	All absent
9	37	F	Incidental finding (1955	Bilateral irregular tonic pupils; normal accommodation	Absent K.J.s, A.J.s, and right B.J. and S.J.
10	37	F	Sudden blurred vision (1954)	Irregular tonic pupil with slow accommodation on the right	Right K.J. and left A.J. sluggish
11	36	M	Sudden blurred and double vision; glare (1954)	Fixed left pupil; tonic pupil, and slow accommodation one year later	Absent S.J.s and A.J.s; K.J.s sluggish
12	35	F	Incidental finding (1955)	Bilateral irregular tonic pupils and slow accommodation on left	Absent T.J.s, K.J.s, and A.J.s
13	26	F	Sudden blurred vision on the left (1954) and on the right (1955). Double vision and headaches	Bilateral changes affecting both pupil and accommodation—paralytic on the right and tonic on the left	All absent except right B.J.
14	22	M	Delayed accommodation and unequal pupils (1954)	Bilateral irregular tonic pupils and slow accommodation	All absent except B.J.s
15	21	F	Sudden ocular pain on the right; enlarged left pupil noted (1955)	Bilateral irregular tonic pupils; normal accommodation	Absent K.J.s and A.J.s

TABLE II

DATA OF HOLMES-ADIE PATIENTS AND MATCHED NORMAL SUBJECTS

Case	Age	Sex	Side	Refraction (dioptres)		Range of Accommodation (dioptres)			Spasm of Accommodation caused by Pilocarpine (dioptres)			Constriction of Pupil caused by Pilocarpine(mm.) in Holmes-Adie Subjects
				Holmes-Adie (1)	Normal (2)	Holmes-Adie (3)	Normal (4)	Difference between (3) and (4)	Holmes-Adie (5)	Normal (6)	Difference between (5) and (6)	
1	57	F	L	+0·9	+1·4	0	0	0	0·7	0	+0·7	2½
2	56	F	R	+3·8	+1·2	0	0	0	1·2	0	+1·2	4
			L	+3·2	+1·2	0	0	0	0·4	0	+0·4	3½
3	53	M	L	−0·1	−1·2	0	0	0	0	0	0	—
4	49	M	R	+0·7	+1·5	0	0·3	−0·3	2·0	0·5	+1·5	4½
5	43	M	L	+0·7	+2·4	1·1	3·1	−2·0	1·2	0·1	+1·1	2
6	42	M	R	−1·4	+2·3	1·0	2·5	−1·5	0·4	0	+0·4	2
7	38	F	R	+0·3	−0·5	5·1	1·5	+3·6	2·6	1·0	+1·6	2
			L	0·0	+0·1	3·3	2·0	+1·3	2·0	1·7	+0·3	3
8	38	F	L	+1·1	−0·3	2·8	1·5	+1·3	2·5	0·6	+1·9	2½
9	37	F	R	0·0	−0·1	5·1	6·7	−1·6	0·8	1·8	−1·0	1½
			L	+1·3	+0·1	2·2	6·5	−4·3	1·0	1·1	−0·1	2½
10	37	F	R	+0·2	−1·7	4·6	5·3	−0·7	0·1	3·1	−3·0	1½
11	36	M	L	−2·7	+0·3	5·2	4·2	+1·0	4·3	0·5	+3·8	3½
12	35	F	L	+3·9	+0·6	2·3	5·4	−3·1	0·3	0·3	0	1
13	26	F	R	+0·5	−0·7	6·2	8·7	−2·5	4·2	0·7	+3·5	3½
			L	+0·7	−0·8	7·2	9·1	−1·9	0·3	1·0	−0·7	3½
14	22	M	R	−0·3	−0·2	—	—	—	5·5	1·4	+4·1	5½
			L	−2·8	−0·3	—	—	—	4·8	2·8	+2·0	4
15	21	F	L	−0·4	+0·3	5·1	7·7	−2·6	0·6	0	+0·6	2½

Methods

(1) **Measurement of Accommodation.**—Accommodation was measured by the difference in refraction of the eye caused by accommodating from distant to near vision. A modification of the coincidence optometer designed by Fincham (1937) was used, both for refracting the eye and for providing the stimulus to accommodation. The refraction of the eye was measured objectively by viewing ophthalmoscopically the retinal image of an illuminated target consisting of a vertical line (Fig. 1). When the eye examined was ametropic, the retinal image fell to one or other side of the principal axis of the eye. This displacement could be seen through the observing system and corrected by altering the position of the target relative to an optometer lens. The required correction represented the refractive error which was read in dioptres on the scale carrying the moving target. The adjustment was made with precision by a coincidence setting. The accommodation stimulus was provided by a second fixation target illuminated by a beam of light,

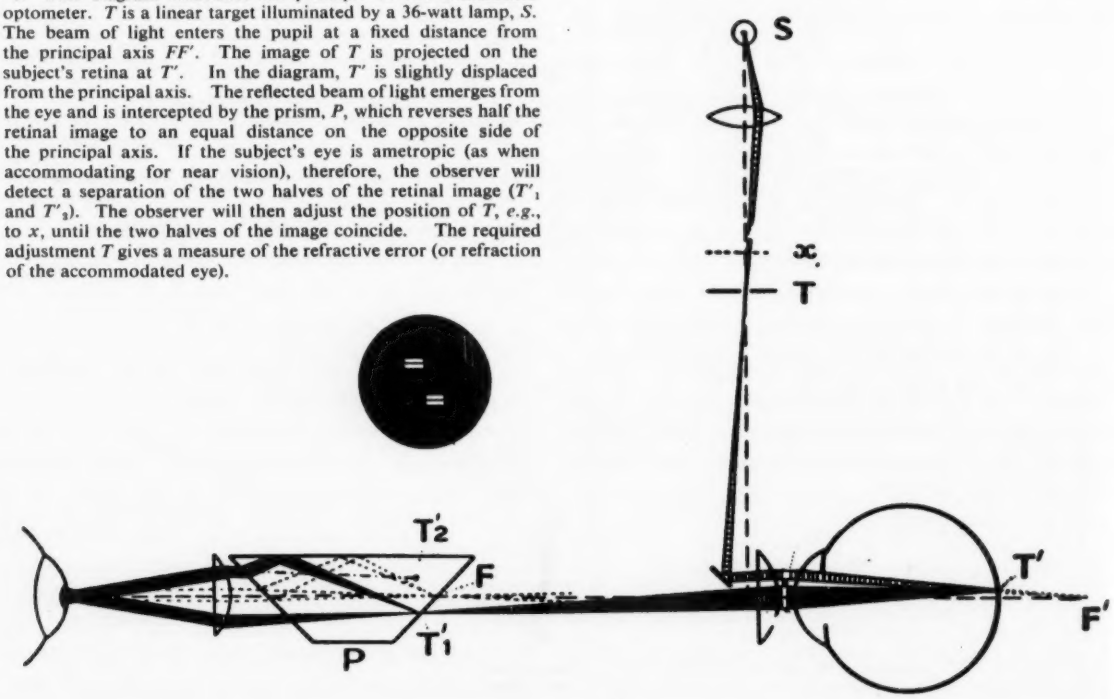

FIG. 1.—This diagram illustrates the principle of the coincidence optometer. *T* is a linear target illuminated by a 36-watt lamp, *S*. The beam of light enters the pupil at a fixed distance from the principal axis *FF'*. The image of *T* is projected on the subject's retina at *T'*. In the diagram, *T'* is slightly displaced from the principal axis. The reflected beam of light emerges from the eye and is intercepted by the prism, *P*, which reverses half the retinal image to an equal distance on the opposite side of the principal axis. If the subject's eye is ametropic (as when accommodating for near vision), therefore, the observer will detect a separation of the two halves of the retinal image (T'_1 and T'_2). The observer will then adjust the position of *T*, *e.g.*, to *x*, until the two halves of the image coincide. The required adjustment *T* gives a measure of the refractive error (or refraction of the accommodated eye).

the vergence of which could be varied. When the light proceeding from the target was parallel, accommodation was relaxed; increasing divergence of light caused a corresponding increase in accommodation. This response is thought to depend on changes in chromatic aberration and on the normal scanning movements of the eye (Fincham, 1951). The fixation target consisted of a detailed black and white pattern which provided a good stimulus to accommodation (Fincham and Walton, 1957). To avoid errors from spherical aberration and from astigmatism, the instrument was centred on the pupil and the same meridian was used before each measurement. Alterations in size of the pupil are likely to cause changes of accommodation by themselves if there result any differences of light vergence. To overcome this important difficulty, the beam of light from the illuminating system was made to enter the pupil at a fixed distance from its centre; a constancy of size (2½ mm. diameter) of the "effective pupil" was thus ensured. A high degree of consistency was attained with this instrument; in a series of four normal subjects, on each of whom the refraction of the relaxed eye was measured on four consecutive days, the standard deviation was 0·14 dioptre.

In order to decide if accommodation was significantly reduced in the Holmes-Adie patients, values were obtained for 18 eyes among 14 patients and compared with those of 18 normal eyes. One patient (Case 14) had an amblyopic left eye and the coincidence optometer did not provide an adequate stimulus to accommodation; he was therefore omitted from the investigation.

(2) **Timing of Accommodation.**—It was not possible to time accommodation with the coincidence optometer, for even normal subjects sometimes failed to respond for several seconds to the stimulus of rapidly altering vergence of light. The delay in accommodating for near or distant vision was also influenced by practice, so that consistent observations were not obtainable.

Graveson's (1949) clinical method was therefore used for measuring the delay in accommodation for near vision in the Holmes-Adie patients. A Jaeger test card which could be read comfortably at a distance greater than the near point was chosen (usually J4 to J8). The patient was asked to change his gaze from a distant object to the Jaeger card, which he held in his hand, and the interval before he could see the print clearly was timed with a stop watch. In a normal subject there is no significant delay.

Estimations were restricted to 11 patients under the age of 45, because presbyopic changes in older patients made timing inaccurate. Among these patients, 16 eyes with tonic pupils were examined.

(3) **Response of Accommodation to Pilocarpine.**—Accommodation was measured with the coincidence optometer. Two drops of 1% pilocarpine nitrate were then instilled from a pipette into the eye, which was later re-examined at five-minute intervals until the maximum effect of the drug was observed. This usually took from 20 to 30 minutes. Fig. 2 shows the effect of this test on a normal subject; for any given strength of accommodative stimulus, there tended to be an enhanced accommodative response after the administration of pilocarpine. This is in agreement with the findings of Fincham (1955), who used eserine instead of pilocarpine. Another feature of the reaction to pilocarpine was an inability of the ciliary muscle to relax fully, as shown by a more myopic reading (X instead of Y in Fig. 2) when the accommodative stimulus was withdrawn. This inability to relax accommodation, or spasm of accommodation, was chosen as a measure of the effect of pilocarpine on the ciliary muscle, and is represented in Fig. 2 by the distance XY (expressed in dioptres).

The effect of pilocarpine was tested in 20 eyes with tonic pupils among 15 Holmes-Adie patients. The induced spasm of accommodation was determined in each abnormal eye and compared with (*a*) the spasm of accommodation in the normal control eye, and (*b*) the response to pilocarpine of the tonic pupil of the same eye. This response was measured by the difference between the pupillary diameters (in mm.) before and after treatment with the drug. The measurement of the pupil was obtained at the same time as accommodation was tested, using a simple Haab pupillometer.

Results

Measurement of Accommodation.—Table II shows how the range of accommodation in the Holmes-Adie patients (column 3) differed from that in the normal controls (column 4). The differences between the two groups are also shown; a negative sign indicates that accommodation was less in the abnormal eye. The means between the abnormal and control groups were compared by a *t* test (for correlated means). The range of accommodation for the Holmes-Adie group was found to be slightly reduced in comparison with that of the normal group, but this difference was found to be not significant ($P = > 0{\cdot}05$).

Timing of Accommodation.—Accommodation for near vision was found to be delayed in 13 out of the 16 eyes examined. The time lag varied from three to 13 seconds (Table III).

TABLE III

DELAY IN ACCOMMODATION FOR NEAR VISION

Case	Side	Delay in Accommodation for Near Vision (sec.)
5	R	7
	L	6
6	R	6
	L	3
7	R	8
	L	13
8	L	< 2
9	R	4
	L	< 2
10	R	3
11	L	3
12	L	7
13	R	10
	L	5
14	L	3
15	L	< 2

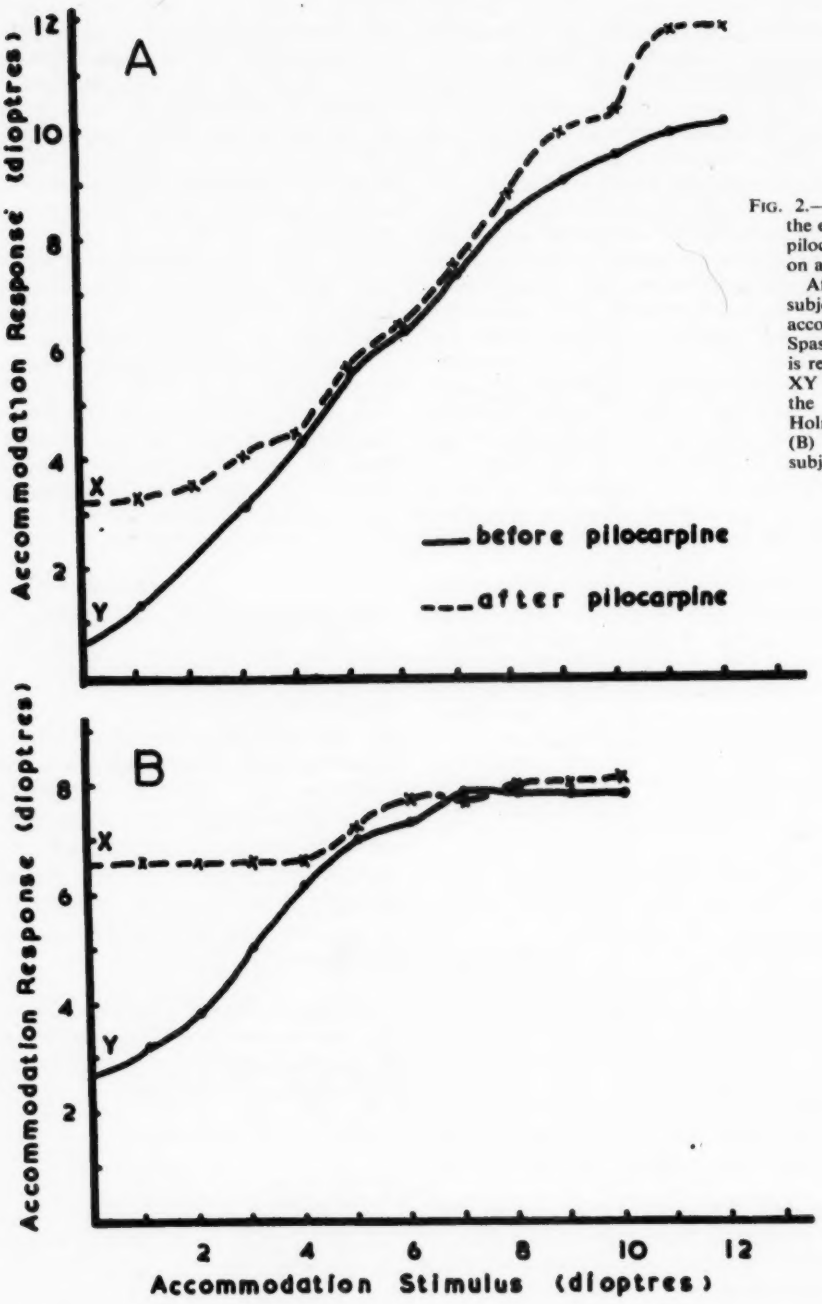

FIG. 2.—Diagram illustrating the effect of instillation of pilocarpine nitrate (1%) on accommodation.

After pilocarpine, the subject is unable to relax accommodation fully. Spasm of accommodation is represented by distance XY which is greater in the patient with the Holmes-Adie syndrome (B) than in the normal subject (A).

Response of Accommodation to Pilocarpine.—Table II shows how the accommodation of Holmes-Adie patients differed in its response to pilocarpine from that of normal subjects: a positive sign indicates that the spasm of accommodation was greater in the abnormal eye. The means between the Holmes-Adie and control group were compared by a *t* test (for correlated means). The spasm of accommodation for the Holmes-Adie group was found to be significantly increased in comparison with the normal group ($P = < 0{\cdot}05$).

A correlation was sought between the effect of pilocarpine on accommodation and on the size of the tonic pupil of the same abnormal eye (Table II). A correlation coefficient of $+ 0{\cdot}59$, significant at the 1% level, was obtained. This indicates that the

sensitivity of the ciliary muscle to pilocarpine tends to increase with that of the sphincter pupillae in the Holmes-Adie syndrome.

Discussion

Fifteen patients with tonic pupils of long standing were examined for remaining signs of abnormal accommodation. It was confirmed that a considerable recovery takes place in the range of accommodation; in fact, no significant difference could be detected between the Holmes-Adie group and the normal controls. In many patients a delay of accommodation develops, which is the defect most easily detected by clinical methods. The group of Holmes-Adie eyes showed a significant increase in sensitivity of the ciliary muscle to pilocarpine. The disturbance of accommodation therefore undergoes a series of changes strictly analogous to those of the tonic pupil; the ciliary muscle eventually recovers its ability to contract and the movement of contraction becomes slower. The ciliary muscle also develops a heightened sensitivity to pilocarpine. This increase in sensitivity bears some relationship to that of the iris. There is good evidence, therefore, for supposing that the abnormal processes affecting the pupil and accommodation are identical. Furthermore, just as the tonic pupil is often preceded by a paralytic one, it is likely that tonic (delayed) accommodation supervenes on a paralysis of accommodation.

It does not follow that every patient with the Holmes-Adie syndrome has at some time had a paralysis of accommodation. In many cases no symptoms are ever noticed, though close enquiry will often elicit the history of a forgotten episode of blurred vision. The development of symptoms depends a great deal on how much the patient relies on his accommodative power. This reliance on accommodation is lessened in myopia and absent in presbyopia, so that myopic and middle-aged subjects may not become aware of abnormal accommodation. With hypermetropia or astigmatism, however, a sudden paralysis of accommodation may prove to be temporarily disabling, especially if it occurs in the young.

Because the tonic reaction is so distinctive and involves both the pupil and accommodation, the understanding of its physiopathology assumes some importance. Two main hypotheses have been formulated to account for the tonic reaction: first, a disturbance of sympathetic function; second, an increased sensitivity of the effector muscles following partial parasympathetic denervation. Evidence has been presented in favour of discarding the first hypothesis (Russell, 1956): neither a lesion nor an overaction of the sympathetic innervation is present. It was shown, on the other hand, that the reaction to pilocarpine is increased in pupils showing the tonic reaction; indeed, the sensitivity to pilocarpine bears a direct relationship to the range of movement caused by convergence, and to the time taken by the pupil to dilate again. Moreover, it was argued that in the tonic pupil parasympathetic function is partly preserved. These facts substantiate the theory put forward by Scheie (1940) that the tonic reaction is due to surviving parasympathetic fibres releasing acetylcholine which diffuses to neighbouring denervated, and therefore sensitized, muscle fibres. Is there any difference between the action of acetylcholine released at nerve endings and that of a parasympathomimetic drug applied locally, as in this investigation ? There would not appear to be, for experimental denervation of the iris results in hypersensitivity to all parasympathomimetic substances, including acetylcholine, whether these substances be injected parenterally or instilled in the conjunctiva (Bender and Weinstein, 1940; Keil and Root, 1941 and 1942; Neidle, 1950). The effect of pilocarpine on the sphincter pupillae and ciliary muscle may be taken to mirror the action of acetylcholine under natural conditions.

The development of paralysis of the pupil and of accommodation with subsequent hypersensitivity to parasympathomimetic drugs places the site of the lesion along the parasympathetic pathway between the third nerve nucleus and the short ciliary nerve endings. It remains uncertain whether the pre- or post-ganglionic nerves are primarily affected, but the evidence favours a post-ganglionic lesion. Thus, there are clinical records of tonic pupils developing after injuries or tumours established as affecting the ciliary ganglion or short ciliary nerves (Axenfeld, 1906; Ohm, 1907; Cords, 1930; Garcin and Kipfer, 1936); a single pathological examination (Ruttner, 1947) has revealed degeneration of ganglion cells in the ciliary ganglion.

There remain many gaps in our knowledge. Experimental work shows that increased sensitivity of the denervated iris develops within a few hours, whereas a much longer period may elapse before the same phenomenon develops after an internal ophthalmoplegia in the human. In one patient observed the tonic reaction of the pupil became manifest only about three months after increased sensitivity to pilocarpine had been detected. An explanation is suggested by the work of Murray and Thompson (1957). They showed that recovery of function after partial sympathectomy in cats depends, not on hypersensitivity, but on collateral sprouting of the surviving sympathetic fibres. By the end of four to eight weeks, the sprouts form new synapses with the denervated ganglion or

effector cells. The phenomenon has not been demonstrated yet in the parasympathetic system, but if it were, it would account more readily for the delay in recovery of pupillary constriction and of accommodation. The tonic reaction would therefore result from two combined sequels to a parasympathetic lesion—hypersensitivity of the effector cells and formation of new connexions by sprouting.

Summary

Accommodation was studied in 15 patients with the Holmes-Adie syndrome in whom ocular abnormalities had been present for 14 months or longer. A coincidence optometer was used to measure the range of accommodation and spasm of accommodation induced by instilling pilocarpine in the conjunctival sac. The delay in accommodating for near vision was measured by simple clinical means. It was found that the disorder of accommodation is very similar to that of the pupil: there is a recovery in accommodative power but contraction of the ciliary muscle is delayed and there develops a sensitivity to the action of pilocarpine. Moreoever, there is a significant correlation between the sensitivity of the ciliary muscle and that of the sphincter pupillae. It is argued that the tonic reaction of the pupil and of accommodation must have a similar mechanism which may be dependent partly on the development of sensitivity of the denervated effector muscle to acetylcholine.

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THE EFFECT OF RESERPINE ON THE DURATION OF MANIC ATTACKS

BY

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Many authors, in advocating special treatments for mania, do not consider the duration of the illness but give instead the number or percentage of those recovered, improved, or unchanged. Smith, Hastings, and Hughes (1943), Ziskind, Somerfeld-Ziskind, and Ziskind (1945), and Schiele and Schneider (1949) advocate E.C.T. General experience with this treatment is that it must often be given intensively and relapses are frequent (Noyes, 1953; Mayer-Gross, Slater, and Roth, 1954; Sargent and Slater, 1948). Hennelly (1936), Kearney and Courtney (1938), and Wilson and Gillman (1938) recommend prolonged narcosis. Lithium is recommended by Cade (1949), Schou, Juel-Nielsen, Strömgren, and Voldby (1954), Glesinger (1954), and Rice (1956), chlorpromazine by Vaughan, Lieberman, and Cook (1955), and Kinross-Wright (1955). With each of these treatments about half the cases remitted during the period of treatment. As most attacks of mania are self-limiting, however, such results do not demonstrate the treatment's efficacy.

The beneficial effect of reserpine on excited patients has been noted by several authors (Barsa and Kline, 1955; Sommerness, Lucero, Hamlon, Erickson, and Matthews, 1955; Altschule, 1956; Hes and Bracha, 1956). Its calming effect in mania, the illness most frequently characterized by excitement, is mentioned specifically by Colombati and Benassi (1954), Flach (1955), Glynn (1955), Kirkpatrick and Saunders (1955), Kinross-Wright (1955), Luttrell and Morrison (1955), Brooks (1956), Sarwer-Foner and Ogle (1956), and Zeller, Graffagnino, Cullen, and Rietman (1956). No author has yet measured its effect on the duration of manic attacks. The efficacy of particular treatments in mania cannot be estimated by the proportion of attacks issuing in " recovery " or " improvement," however. The majority terminate without special treatment and it is imperative, therefore, to take into account the duration of the attack which is, at present, the only measurable index of the treatment's effect. This is undertaken in the present study to make a more precise assessment of reserpine in the treatment of mania and to compare it with other treatments.

Case Material and Method

For this investigation two groups of manic attacks occurring in female patients are compared. The first group (Group 1) consisted of 19 attacks occurring in 18 patients, whose average age was 43·7 years with a range of 17 to 68 years (S.D. = 11·5); the patients comprised all the female cases diagnosed as suffering from mania and admitted to a county mental hospital (St. John's Hospital, Stone, Bucks.) between December 3, 1955, and February 6, 1957. The only specific treatment given during the attacks included in Group 1 was the administration of reserpine. The initial dose varied from 8 mg. to 15 mg. daily; 8 mg. was the most frequent initial dose and it was usually given intramuscularly. This was replaced by oral administration within a few days and the dose reduced as the patient improved. Once the dose was increased to 20 mg. daily for a few days. Two cases improved shortly after admission and received no specific treatment. The duration of treatment ranged from two to 10 weeks. The most frequent period of treatment was six to seven weeks.

The second group (Group 2) consisted of 44 attacks of mania in 32 patients whose average age was 46·6 years with a range of 20 to 72 years (S.D. = 16·1). These were all the female patients suffering from mania discharged from St. John's Hospital during the five years 1951-55. Three attacks included in Group 1 occurred in patients who had had earlier attacks of mania for which they were admitted to other hospitals than St. John's. These earlier attacks occurred in the period 1951-52 and are included in Group 2. The attacks in Group 2 were treated by various methods: prolonged narcosis (four attacks); E.C.T. (nine attacks); insulin coma therapy (three attacks); chlorpromazine (two attacks). The majority had no specific treatment (26 attacks).

Mania (and hypomania) is possibly the most protean of the major psychiatric syndromes and the diagnosis is correspondingly difficult (Deron, 1928). The features commonly relied on are increased motor activity, increased talk, rapid thought with facility of association, distractibility, euphoric or grandiose mood, often labile and tending to anger. In distinction from schizophrenia, thought content and mood are usually consonant; delusions do occur, but are usually unsystematized and are less common than distortions arising from features

of the patient's circumstances and environment which he finds displeasing. A setting of clear consciousness is present except in severe cases where delirium may occur and hallucinations be present (Lewis, 1956; Mayer-Gross *et al.*, 1954). The cases selected here conformed to this general picture. The majority were seen by the author during the attack and all the case records were examined by him. One patient who was of low average intelligence (I.Q. 84) suffered from petit mal. In no other case was any complicating factor known to be present. Previous or subsequent attacks of affective illness, necessitating the patient's admission to hospital and resulting in discharge, occurred in 41 of the 50 patients. In six attacks (one in Group 1, five in Group 2), there was a depressive spell, three at the beginning, two at the end, and one interpolated in the attack. The longest of these did not exceed one month and they are included in the duration of the attack.

The duration of hospital stay in each attack was estimated in both groups which were then compared in this respect. The duration of hospital stay was taken as the period between the date of admission to hospital and the date of leaving. Three cases were exceptional: in Group 1 a patient was treated with chlorpromazine and relapsed. She was then treated with reserpine and the duration of the attack of mania is dated from the start of this treatment. In Group 2 one patient was admitted for six weeks to a general hospital for the treatment of diabetes. She was mentally ill throughout this time, and, proving unmanageable, was returned to the mental hospital. The duration of the manic attack was here calculated from the date of first admission to the mental hospital to the date of her discharge home and includes the period spent in the general hospital. A second patient discharged herself while still unwell and was admitted as a certified patient 21 days later. The duration of hospital stay was here calculated from the date of the first admission until the date of the second discharge. It would have been most satisfactory to compare both groups in respect of the total duration of the attack, but this was not possible as the dates of admission and discharge from hospital are the only temporal features of the attack which are certain in every case.

The time between the onset of an attack and the patient's discharge from hospital can be divided into three periods: first, that between the onset of the attack and admission to hospital; second, that between admission to hospital and recovery from the attack; third, that between recovery and discharge from hospital. The duration of the attack differs from the duration of hospital stay in respect of the first and third of these periods whose mean duration is therefore compared in the two groups of manic attacks. The estimation of the first period is less satisfactory than of the third, however, as the date of onset of an attack was seldom clearly stated in the clinical notes. This is understandable as it was not of immediate practical importance to the receiving doctor who, in addition, depended upon the retrospection of the patient or of a witness. It is given as an answer to one of the questions in the statement of particulars of both voluntary and certified patients, and it is from this source that it has been obtained by the author in the majority of cases. Recovery, on the other hand, took place in hospital and was of such immediate consequence, *e.g.*, in determining the date of discharge, that it was noted in all but eight attacks (one in Group 1, seven in Group 2). In five attacks the patients discharged themselves before recovery took place, and in three the notes were incomplete.

Results

The mean duration of hospital stay in the group treated with reserpine is 11·0 weeks (range 3-22, S.D. = 11·3) and in the group in which this treatment was not used 19·0 weeks (range 3-50, S.D. = 11·4) and this difference is significant ($t = 2{\cdot}90$, $P < 0{\cdot}01$, d.f. = 61).

The date of onset was determined in 17 out of 19 attacks in Group 1, and in 34 out of 44 attacks in Group 2, and the period between this date and hospital admission was calculated in each case. The mean period between onset and date of admission is 3·2 weeks for Group 1 (range 1-13, S.D. = 3·2) and 2·2 weeks for Group 2 (range 1-12, S.D. = 2·3).

The period between recovery and date of discharge was calculated for 18 out of 19 attacks in Group 1 and for 37 out of 44 attacks in Group 2. The mean is 4·9 weeks for Group 1 (range 1-13, S.D. = 3·5) and 4·5 weeks for Group 2 (range 1-19, S.D. = 4·1).

A second opportunity of comparing attacks of mania treated with reserpine with those otherwise treated presented itself in eight patients whose illness was recurrent. Each of these patients had one attack treated with reserpine in St. John's Hospital, while previous attacks (a few of which had been spent in other mental hospitals) had not been treated with reserpine. Table I shows, for each of the eight

TABLE I

DURATION OF ATTACKS OF MANIA TREATED WITH RESERPINE AND BY OTHER METHODS IN PATIENTS WITH RECURRENT ATTACKS*

Patient	Dates of Admission	Duration of Hospital Stay (weeks)
1	9. 7.51	15
	14. 8.53	16
	10. 8.56	3
2	26. 3.52	9
	16. 8.56	14
3	20. 8.51	14
	13. 5.53	44
	23. 5.55	10
	1.10.56	4
4	5. 6.55	6
	11. 9.55	14
	7.10.56	8
5	7 .1.52	28
	8.12.53	22
	13. 7.56	12
6	3. 7.55	56
	31. 7.56	14
7	15. 3.40	28
	26. 2.51	19
	3.12.55	17
8	2. 4.51	50
	4. 3.53	15
	2.11.54	7
	5. 6.57	8

*The last attack in each case is that treated by reserpine.

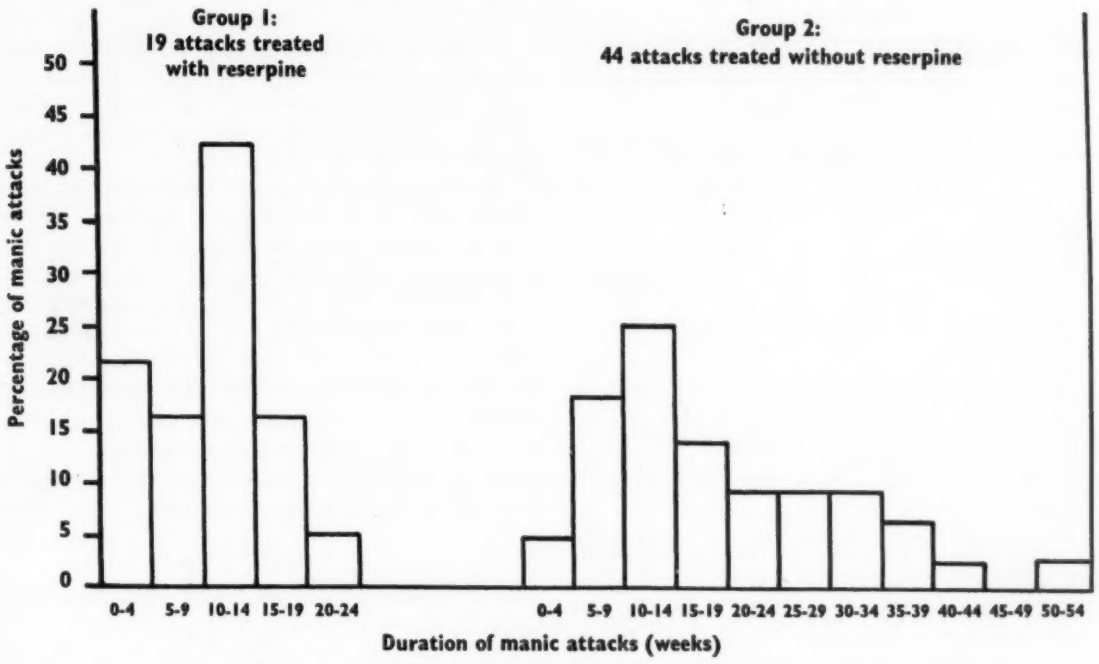

FIG. 1.—Frequency distribution of duration of hospital stay of manic attacks.

patients, the duration of the manic attack treated with reserpine and the duration of those attacks treated by other methods. Sixteen comparisons are possible, in individual patients, between manic attacks treated with reserpine and those treated otherwise, and in 13 the attack treated with reserpine is the shorter, the average difference being 13·1 weeks (taking sign into account). The numbers here are too small for statistical treatment, but the differences are in the same direction as those shown previously.

Discussion

The results demonstrate that reserpine shortens the duration of manic attacks. The histograms in Fig. 1 show the frequency distribution of the durations of attacks of mania expressed as a percentage for each group of attacks. It can be seen that in the group treated with reserpine the proportion of excessively long attacks is less and of short attacks more than in the group in which reserpine was not used.

It would have been ideal but impracticable to have the reserpine-treated group and the control group contemporary because of the infrequent occurrence of manic attacks. It may be objected that the two groups are not comparable because policy with regard to discharge may have altered during the period (1951-57) in which the subjects of this investigation left the hospital. The difference between the two groups cannot be accounted for by more hasty discharge of the patients in Group 1, however, as the mean duration of the period between recovery and discharge is the same for both groups. It must be admitted that the date of recovery might be more promptly noted in the reserpine-treated group who were under surveillance by the author because of their novel treatment. Little weight can be placed on the figures for the duration of the period between the onset of the attack and admission to hospital, but, such as they are, the disparity between them could not account for the difference in average duration of hospital stay between the two groups. In any case, it is conjectural what effect the length of the period between the onset of the attack and admission to hospital has on the duration of the period between admission and recovery. More general changes in hospital administration and function may possibly influence the rate of recovery. If, however, Group 2 is divided into periods 1951-52 and 1953-55, each containing 22 attacks, the average duration of stay in hospital during the early period (1951-52) is 18·9 weeks and during the later period (1953-55) is 19·2 weeks.

The comparatively lesser duration of hospital stay in the majority of the attacks treated with reserpine, in those patients with recurrent attacks, supports the evidence already presented that the effect of reserpine is to shorten manic attacks.

Table II shows the duration of stay in hospital of

TABLE II

DURATION OF HOSPITAL STAY IN MANIC ATTACKS AS PUBLISHED BY SEVERAL AUTHORS

Author	Average Duration of Hospital Stay (weeks)		No. of Cases
	No Specified Treatment	Specific Treatment	
Rennie (1942)	20·6	—	42
Tómasson (1936)	25·7	—	24
"	—	15·4	21
Panse (1924)	27·3	—	—
Lundquist (1945)	31·3	—	103
Wertham (1929)	34·6	—	2,000
Malzberg (1929)	35·3	—	2,000
Oltman and Friedman (1950)	42·0	—	318
"	—	18·2*	58
Morrow and King (1949)	—	8·4†	46
Present author	19·0	—	44
"	—	11·0	19

*Measured from start of treatment.

†Includes only those patients who recovered during period of treatment.

patients with manic attacks taken or derived from figures published by several authors. These data were collected under varying conditions and no strict comparison is possible. The lower average figures in the small groups of attacks are possibly accounted for by more careful selection of cases and more stringent diagnostic criteria. It can be seen that only two authors compare the duration of attacks in treated and untreated groups. Tómasson (1936) gives a careful account of the duration of manic attacks in 21 cases treated with ephedrine and acetylcholine. The average duration of hospital stay for these patients was 15·4 weeks which compares favourably with other patients not treated by his method. There are, unfortunately, no other published accounts of this treatment, although Tómasson still uses it (personal communication, 1957). Oltman and Friedman (1950) give the frequency distribution of the duration of the period between the start of E.C.T. and discharge from hospital in 58 cases, which gives an average of 18·2 weeks. The average for cases not treated with E.C.T. is 42·0 weeks, but it should be noted that this figure refers to the total duration of hospital stay. Morrow and King (1949) give an average stay in hospital of 8·4 weeks for 46 patients suffering manic attacks. This figure, however, includes only those patients where recovery took place during the period of treatment and not those in whom it did not. Moreover, these patients were in a private clinic, and it cannot be doubted that the expense to the patient would influence the therapist in favour of early discharge.

Summary

A clinical trial is described in which the average duration of hospital stay in 19 manic attacks treated with reserpine is compared with that in 44 manic attacks not treated with this drug and is found to be significantly smaller.

The two groups were not contemporary, but it is shown that it is improbable that this difference between them could be accounted for by shorter hospital stay following recovery in the group treated with reserpine or by other changes in hospital policy.

In eight patients who had had several attacks of mania the attack treated with reserpine was, in the majority of instances, shorter than the patients' other attacks.

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A CONTROLLED TRIAL OF MEPROBAMATE IN ANXIOUS OUT-PATIENTS

BY

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Meprobamate was first synthesized by Ludwig and Piech in 1951. Its pharmacological properties have been studied by Berger, who described it as an interneuronal blocking agent related to mephenesin (Berger, 1954; Berger, Hendley, Ludwig, and Lynes, 1956). He noted that when it was administered to monkeys they became more manageable and did not demonstrate fear when handled. Early reports of its clinical use were favourable, patients experiencing relief from anxiety, tension, and tension headache (Borrus, 1955; Selling, 1955). Some later reports have not shown the same degree of success. West and Fernandes da Fonseca (1956) found a significant degree of improvement in patients receiving meprobamate compared with placebo, whereas Raymond, Lucas, Beesley, O'Connell, and Fraser Roberts (1957) found no significant difference from treatment with placebo. Folkson (1957) found only a small number of patients improved while receiving meprobamate and there was an appreciable incidence of toxic effects. Reports of such toxic effects have become more frequent as the use of this compound has increased (Friedman and Marmelzat, 1956; Council on Drugs of American Medical Association, 1957). The aim of the present study was to determine if meprobamate has a beneficial effect on anxious patients and, if possible, to observe which symptoms improve.

Method

The design of this trial was similar to that used by Davies and Shepherd (1955) in a trial of reserpine. The patients studied were attending the Out-patient Department for treatment, and their symptoms included anxiety and, in the majority, a feeling of tension. Twenty men and 20 women, who were thought to be suitable for treatment with meprobamate and whose ages were between 18 and 60, were selected. At the initial interview a record was made of the duration of the present condition, of any previous mental illness, and of previous treatment such as drugs, psychotherapy, or E.C.T. The symptoms of anxiety, feelings of tension, depression, photic or compulsive phenomena, insomnia, anorexia, and somatic pains, including headache, were assessed as severe, moderate, mild, slight, or absent. Also, based on all the information available, the patients were assessed as those liable to retain many symptoms or those liable to become relatively free of symptoms.

The patients received either meprobamate, 400 mg. q.d.s., or placebo tablets of identical appearance, q.d.s., throughout the trial period of four weeks. The tablets were dispensed to the individuals in a random order known to the pharmacist. The patients were told that they were to receive these tablets for four weeks to see if it would help them. During the trial they were seen at weekly intervals to note their progress and to give supportive psychotherapy if indicated. Any unwanted side-effects of the medication were recorded but in no case were these serious enough for treatment to be stopped. At the end of the four weeks the change in the patient was assessed. He was required to indicate on a form if he considered himself in general to be much better, better, unchanged, worse, or much worse. The doctor also estimated the general change in the patient and assessed the change in the individual symptoms, *i.e.*, anxiety, depression, as above. Changes in the patients' circumstances or attitude during this period were considered; the changes might be environmental or of a psychotherapeutic nature occurring in the course of the five interviews. Until the end of the whole trial and all the assessments were completed the pharmacist did not inform the doctor which tablets the patients received.

Comparison of Groups

The original data and assessments of the patients in the meprobamate and placebo groups are shown in Tables I and II.

Inspection of Table I shows that the random allocation of the patients into the two groups fulfilled its purpose in distributing them evenly, according to these criteria. The incidence and the severity of the symptoms (Table II) were not significantly different in the two groups. The method of comparison is described below where the results are considered; it has not only been applied to the whole group of patients shown in Table II, but also to the group of patients who completed the trial.

The assessment of psychotherapeutic or environmental change during the trial showed no significant

TABLE I

DATA OF THE TWO GROUPS AT START OF TRIAL

	Meprobamate	Placebo
Age	18–52 yr. (mean 31·5)	20–57 yr. (mean 32·5)
Sex	10 M., 10 F.	10 M., 10 F.
History of previous mental illness	9	10
Duration of present illness	1 month–10 yr. (mean 18 mth.)	1 month–11 yr. (mean 16 mth.)
Previous Treatment:	12	13
In-patient	2	2
E.C.T.	–	1
Barbiturates	8	7
Other medication	9	11
Psychotherapy	5	3
Prognosis:		
Retain many symptoms	5	7
Retain few symptoms	15	13

TABLE II

SYMPTOM ASSESSMENTS OF THE TWO GROUPS AT START OF TRIAL

Symptom	Group	Nil	Slight	Mild	Moderate	Severe
Anxiety	Meprobamate	—	—	10	10	—
	Placebo	—	2	11	7	—
Tension	Meprobamate	—	5	7	8	—
	Placebo	1	2	11	6	—
Depression	Meprobamate	3	8	8	1	—
	Placebo	3	12	5	—	—
Insomnia	Meprobamate	3	8	6	3	—
	Placebo	6	4	7	3	—
Anorexia	Meprobamate	9	4	7	—	—
	Placebo	11	4	4	1	—
Compulsions or phobias	Meprobamate	7	2	10	1	—
	Placebo	12	3	3	1	1
Somatic pains (including headaches)	Meprobamate	6	7	7	—	—
	Placebo	5	10	5	—	—

difference between those receiving meprobamate and those receiving the placebo. To ascertain which patients have gained from psychotherapy during five interviews is a difficult exercise. However, if there was an obvious gain of insight into psychological factors relevant in causing the symptoms, or if there was a rewarding discussion of significant emotional problems, these were accepted. For example, a man, who was unofficially engaged, numbered among his symptoms a fear that he had venereal disease. During the trial period he made the decision that he did not want to get married and told the woman concerned; he then lost this symptom. Using these criteria, three of the " meprobamate group " were scored (these three improved) and five of the placebo group (four of these improved). Environmental changes were scored, *e.g.*, a week's holiday or resignation from a worrying job with a cantankerous employer. Four of the " meprobamate group " had such a change (one improving) and four of the control group (two improving).

Results

Of the 40 patients studied, four failed to complete the four weeks on the tablets. In three of them, all receiving meprobamate, it was due to admission to hospital either from worsening of their state or because they could no longer be maintained at home. The other patient, owing to an error in administration, only took the placebo for two weeks. The three patients admitted to hospital after periods of four, nine, and 21 days were followed up and the information received indicated that they were not improved while taking meprobamate over this period. The patient taking placebo for two weeks only was normally assessed at the end of this time. Three patients did not attend for one of their weekly visits for various reasons; one could only attend at a late hour and so another doctor saw him for three of his visits, and one patient, because of the severity of his phobia, could not attend on two occasions, but his wife came to report his progress and obtain the tablets. These last-mentioned five patients otherwise conformed with the design of the trial. In determining the results, therefore, the group has been studied as one of 36 completing the trial. If the four not completing the trial were not taken into account, this might, in some instances, favour the results of the " meprobamate group " by the exclusion of three who showed no improvement before leaving the trial. Where relevant the results have been assessed for the whole 40, employing for these results the state of the patient when he stopped treatment.

It may be seen in Table III that, in general, the

TABLE III

ASSESSMENT OF CHANGE IN GENERAL STATE OF TWO GROUPS AT END OF TRIAL

General Assessment		Much Better	Better	Unchanged	Worse	Much Worse
By doctor	Meprobamate	4	10	3	—	—
	Placebo	2	9	7	1	—
By patient	Meprobamate	3	11	2	1	—
	Placebo	4	6	8	1	—

TABLE IV

ASSESSMENT OF CHANGE IN SYMPTOMS OF TWO GROUPS AT END OF TRIAL

Symptom	Group	Much Better	Better	Unchanged	Worse	Much Worse	N.A.
Anxiety	Meprobamate	2	13	2	—	—	—
	Placebo	1	7	11	—	—	—
Tension	Meprobamate	6	7	4	—	—	—
	Placebo	2	8	8	—	—	1
Depression	Meprobamate	1	6	6	1	—	3
	Placebo	—	9	6	1	—	3
Insomnia	Meprobamate	2	9	3	—	—	3
	Placebo	1	7	5	—	—	6
Anorexia	Meprobamate	1	4	3	—	—	9
	Placebo	—	4	4	—	—	11
Compulsions or phobias	Meprobamate	1	5	6	—	—	5
	Placebo	—	1	6	2	—	10
Somatic pains (including headaches)	Meprobamate	2	3	8	—	—	4
	Placebo	—	3	12	1	—	3

patients improved subjectively and objectively. The two groups were compared statistically by comparing the proportions improved in each. For these comparisons arc sine transformation of the square roots of the proportions (to achieve normality of distribution) were employed and the critical ratios (C.R.) calculated (Davies, 1954). The probability levels (P) of these critical ratios were then noted. In some instances χ^2 tests, using Yates' correction, were also used, the two methods, as expected, showing general agreement. In Table III the incidence of improvement as assessed by the doctor was not significantly greater in the " meprobamate group " ($P > 0{\cdot}05$), although this group tended to do better. In this comparison, for statistical purposes, the patients were considered to be either improved or unimproved and a one-tail test used. The self-rating of the 36 patients showed significantly better response with meprobamate (C.R. = 1·98; $0{\cdot}02 < P < 0{\cdot}05$). If the other four patients are taken into account the difference is not significant.

Table IV shows that all symptoms tend to improve during the trial and with one exception those receiving meprobamate have a greater tendency to improve. The exception is the symptom of depression, where the greater number of patients improved with placebo. Anxiety, phobic-compulsive phenomena, and perhaps feelings of tension are improved in the meprobamate group to a statistically significant greater degree. Anxiety in those 36 completing the trial showed a highly significant improvement with meprobamate, 15 out of 17 improving with meprobamate and only eight out of 19 with placebo (C.R. = 3; $P < 0{\cdot}01$). Even if the other four of the total series, including the three on meprobamate admitted to hospital unimproved, are taken into account the improvement is still significant (C.R. = 2·29; $0{\cdot}01 < P < 0{\cdot}025$). The number of patients whose symptoms of tension improved to the rating of " much better " was significantly greater with meprobamate in those completing the trial (C.R. = 1·74; $0{\cdot}01 < P < 0{\cdot}05$), but just fails to reach this level if those admitted to hospital are taken into account as unimproved (C.R. = 1·6; $P > 0{\cdot}05$). The phobic and compulsive group of symptoms was improved in a greater proportion of patients with meprobamate (C.R. = 2·01; $0{\cdot}01 < P < 0{\cdot}05$) and it still reaches the 5% level of significance if all 40 patients are considered (C.R. = 1·86; one-tail test; $0{\cdot}01 < P < 0{\cdot}05$). Sleep, appetite, somatic pains, which include headaches and depression, did not show any significant degree of difference between the two groups.

The side-effect most often noticed by the patient was drowsiness, nine of the 20 patients receiving 400 mg. meprobamate q.d.s. felt drowsy for periods from two days up to two weeks, by which time the effect had worn off. One patient receiving placebo complained of the same thing for a few days. This difference between the two groups is significant ($\chi^2 = 6{\cdot}5$; d.f. = 1; $P < 0{\cdot}02$). One patient on meprobamate complained of a dry throat and aching legs in addition to his many somatic symptoms. One patient with similar somatic symptoms felt shivery and defaecated more frequently after taking the placebo tablets. None of the more serious

toxic effects which have been reported with meprobamate occurred in these 20 patients.

Discussion

The general or overall assessment in these patients showed no significantly greater degree of improvement in those receiving meprobamate compared with those receiving placebo. The exception to this is the result of the self-rating by the 36 patients who completed the trial. One hesitates to ascribe too much importance to this finding, as, discounting three patients receiving meprobamate and yet requiring admission to hospital for psychiatric symptoms, it would favour the result of this medication. This part of the result of the trial is in accord with the findings of Raymond *et al.* (1957). However, their paper, based on the patients' subjective estimate of the effect of the tablets (very good, good, none, poor, or very poor) did not bring out another aspect shown in the present study, that certain symptoms are improved. Anxiety has been alleviated to a significant degree, in agreement with many papers, including the trial described by West and Fernandes da Fonseca (1956). Similarly, the feeling of tension is decreased in these patients as described frequently in other reports (Heller, Walton, and Black, 1957). As the phobic-compulsive disorders do not usually respond readily to treatment, any drug which relieves distress in these conditions is worthy of note. When considering the individuals in the group with these symptoms, those improving were those with fears of travelling, of crowds, of being shut in, or ceasing to breathe. Of course, not all of these patients improved, but none of the three with compulsions, *e.g.*, checking taps or the contents of a handbag, altered. The symptoms which did improve in this phobic-compulsive group were those most closely related to anxiety. Regarding the symptom of depression, the results indicate that this symptom may do better with placebo than with meprobamate but the difference is not statistically significant. Of those completing four weeks on treatment, one having placebo and one having meprobamate, were rated as becoming more depressed. Two of those patients receiving meprobamate, who were admitted to hospital during the trial, were reported to have become more depressed. Headaches were not improved to a significant degree, contrary to the findings of Selling (1955).

No side-effects seriously affecting the patients' health were noted in this trial. Almost half of the patients taking meprobamate complained of drowsiness during the first two weeks, after which time it disappeared. A controlled trial of hypnotics has shown that meprobamate has a hypnotic effect (Hinton and Marley, to be published). This does not substantiate the claim that it tranquillizes without impairing the alertness of the patient. However, its effect in relieving anxiety, feelings of tension, and the irrational fears in phobic conditions has been shown.

Summary

A controlled trial treating 40 anxious out-patients with either meprobamate or a placebo for four weeks is described. The general improvement and the change in the individual symptoms were studied.

The general improvement with meprobamate failed to reach a significantly higher level than improvement with the placebo.

There was a significantly greater alleviation of anxiety, feelings of tension, and phobic symptoms with meprobamate. Insomnia, anorexia, somatic symptoms, including headaches, were not significantly improved by meprobamate.

Depression in the placebo group improved further than in the meprobamate group, but not to a statistically significant degree.

Almost half of those receiving meprobamate were drowsy during the first fortnight. No serious toxic effects were noted.

I would like to thank Dr. D. L. Davies, who suggested the design of this trial and whose help has made it possible. My thanks are also due to the consultants of the Maudsley Hospital who have permitted me to treat their patients; to Dr. A. E. Maxwell for his advice on the statistical analysis; to Mr. W. T. Brookes, the pharmacist, for his willing cooperation, and to Lederle Laboratories Division for supplying " miltown " tablets and the placebo.

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MYELOID CELLS IN CEREBROSPINAL FLUID

BY

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The cells of cerebrospinal fluid are usually examined in a Fuchs-Rosenthal chamber using a nuclear stain. By this means it is possible to distinguish between polymorphonuclear leucocytes and lymphocytes, but difficulties arise when other types of cell are predominant.

If films can be made of a quality comparable with that expected for haematological diagnosis, various other cell types are found. Besides neutrophil polymorphonuclears and small lymphocytes, one sees many cells of the lymphoid and plasma cell series, eosinophils, occasionally basophils, and a variety of monocytoid cells and macrophages (some of which may possibly be derived from the leptomeninges). For illustrations the reader is referred to Szécsi (1911), Rotstadt (1916), and Chalier and Étienne-Martin (1935). In rare cases tumour cells can be identified (Spriggs, 1954) or the abnormal cells of leukaemia (Spriggs and Boddington, 1958).

A surprising finding, which does not appear to have been previously described, is the presence of promyelocytes, myelocytes, and normoblasts in the cerebrospinal fluid of non-leukaemic cases. There are only some very doubtful instances in the literature. For example, Szécsi's (1911) coloured drawings include some granular cells referred to in the caption as lymphoidocytes; Plaut, Rehm, and Schottmüller (1913) mentioned a case in which granular " plasma " cells were present, the granules staining red-brown with Schridde's method (aniline acid fuchsin); and Rotstadt's (1916) coloured plate shows in row IV, Cell 7, something which might be a myelocyte, interpreted as " *? Mastzelle* ".

We have observed four cases in which myeloid cells occurred in the cerebrospinal fluid in conditions other than leukaemia, and brief case histories are given below. The method of preparing films is given by Spriggs and Boddington (1958).

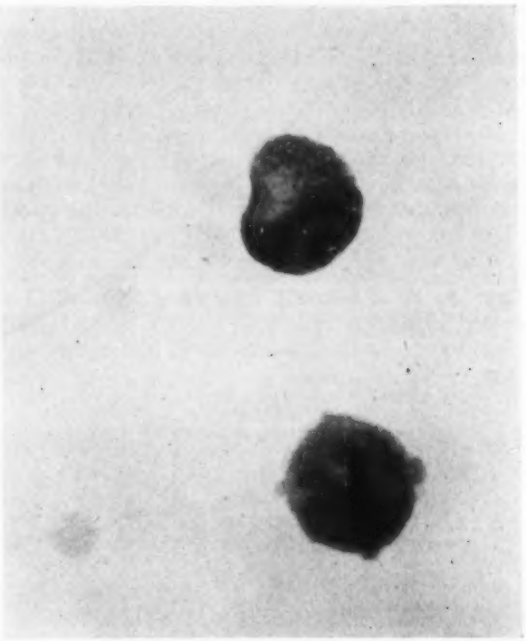

FIG. 1.—Case 1: The two white cells are (*top*) a neutrophil myelocyte and (*bottom*) a promyelocyte in a film of cerebrospinal fluid deposit × 1,180).

Case Reports

Case 1.—A man of 54 was admitted to the Nuffield Department of Neurosurgery (Reg. No. 5238) with a history of " blackouts ", right-sided weakness, and deteriorating vision. He was found to have a right hemiparesis. The lumbar cerebrospinal fluid was under a pressure of over 300 mm. H_2O; the protein content was 250 mg. per 100 ml. The white cell count was 88/c.mm. and the red cell count 96/c.mm. Because some unidentified cells were found in the counting chamber, a film was made (Fig. 1) and a differential white cell count was as follows: " Blast cells " 4%, promyelocytes 7%, myelocytes 25%, band cells 17%, segmented neutrophils 31%, lymphocytes 14%, monocytes 1%, and normoblasts 1%.

The patient's blood showed no abnormality. A left angiogram showed a large fronto-parietal lesion, and a meningioma weighing 99 g. was removed a few days later. The patient's recovery was uneventful, and he was well four years later.

Case 2.—A boy aged 10 was admitted to the Nuffield Department of Neurosurgery (Reg. No. 179906) with paroxysmal headaches, vomiting, and diplopia. A cerebellar exploration revealed a cerebellar tumour, and

he was treated by radiotherapy. Seven months after the operation he was readmitted with hemiparesis and hemianopia. A lumbar puncture was performed in the theatre as well as a puncture of the left ventricle and an aspiration biopsy. The tumour was a glioblastoma multiforme, and tumour cells were found in the left ventricular fluid. The lumbar cerebrospinal fluid had a protein content of over 1,000 mg. per 100 ml., no sugar, and a white cell count of 22/c.mm. with 750 red cells/c.mm. A differential count on a stained film was as follows:—Promyelocytes 1%, myelocytes (neutrophil 8%, eosinophil 1%), polymorphonuclears (neutrophil 35%, eosinophil 1%), lymphocytes 28%, monocytes 24%, normoblasts 1%, unidentified 1%.

No blood count was done at this time, but there was no reason to suspect leukaemia. The boy died a few days later.

At necropsy (P.M. No. 374/54) a large tumour was found involving the left frontal, parietal, and temporal lobes, and this had " seeded " in the dura and down the spinal cord. There was some opacity of the vertical and basal meninges, but histologically there was no evidence of invasion by tumour cells in these areas, and no myeloid tissue was found in the meninges.

Case 3.—A 69-year-old man (Reg. No. 4015) was admitted in cardiac failure to Cowley Road Hospital; he was incontinent and aphasic and had a right hemiparesis.

FIG. 2.—Case 3: A neutrophil myelocyte in a film of cerebrospinal fluid deposit (× 1,180).

Cerebrospinal fluid obtained by lumbar puncture had a protein content of 30 mg. per 100 ml. and three white cells per c.mm. Films (Fig. 2) showed fewer than 100 identifiable cells, but a differential count on 80 cells was as follows:—Promyelocytes 5%, myelocytes 26%, neutrophil polymorphonuclears 32%, lymphocytes 33%, normoblasts 4%.

A blood count and film showed no abnormality, and a second lumbar puncture 16 days after the first showed a normal fluid without myelocytes. The patient died seven

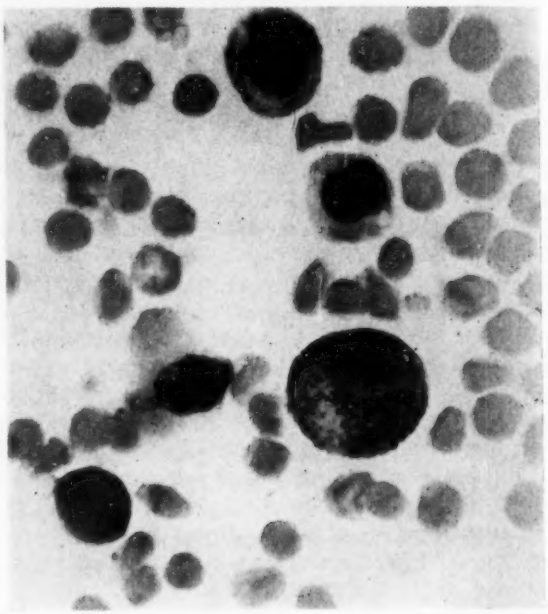

FIG. 3.—Case 4: Field from a film of cerebrospinal fluid deposit showing immature granular cells and (at about 10 o'clock) a normoblast (× 1,180).

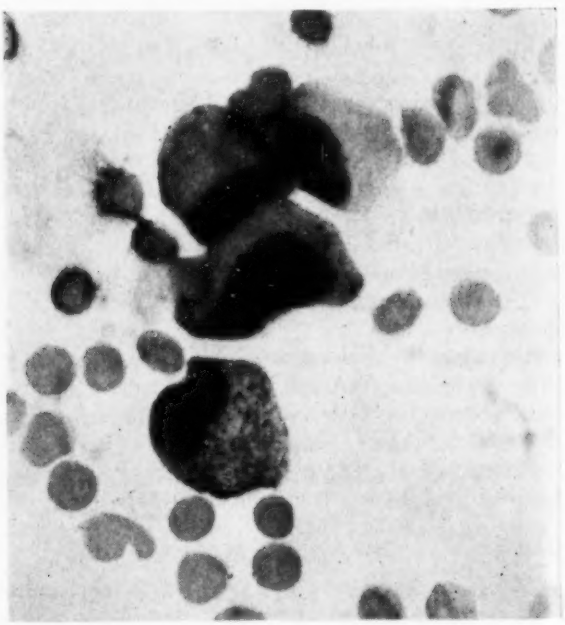

FIG. 4.—Case 4: Myelocytes and red cells in a film of cerebrospinal fluid deposit (× 1,180).

weeks later and necropsy revealed multiple cerebral thromboses. No explanation for the abnormal findings in the cerebrospinal fluid was forthcoming.

Case 4.—A woman (Reg. No. 4280) of 85 was admitted to the Cowley Road Hospital with confusion, considered to be due to cerebral atherosclerosis, and hypertension. The haemoglobin level was 88% and a stained blood film showed no abnormality. A lumbar puncture was performed, and the cerebrospinal fluid had a protein content of 45 mg. per 100 ml., with 16 white cells and 650 red cells per c.mm. A differential count on a stained film of cerebrospinal fluid deposit (Figs. 3 and 4) showed:—Myeloblasts 1%, promyelocytes 4%, myelocytes 37% (neutrophil), polymorphonuclears (neutrophil 41%, eosinophil 2%), lymphocytes 7%, monocytes 3%, normoblasts (basophilic 3%, polychromatic 2%).

A second specimen of cerebrospinal fluid obtained 14 days later had a protein content of 45 mg. per 100 ml., 5 red cells per c.mm., and no white cells. The patient was discharged improved.

Discussion

In the four cases described, the cytological findings in the cerebrospinal fluid seemed to be clinically irrelevant, and in Cases 3 and 4 a second puncture produced normal cerebrospinal fluid without immature myeloid cells. It therefore seems most probable that the cells in question reached the cerebrospinal fluid accidentally as a result of the operator inadvertently puncturing a bone. The posterior surface of a lumbar vertebral body has only a very thin cortex (Fig. 5), and I have found, experimenting on a cadaver, that the marrow can be penetrated by this route with only a very slight sensation of resistance. A point in favour of this hypothesis was the presence in all four cases of moderate numbers of red cells. These are not usually present in such numbers in cases of leukaemia with raised cerebrospinal fluid cell counts (Spriggs and Boddington, 1958). Also the differential counts in the present series of cases are not improbable for small samples of normal bone marrow, allowing for the variations caused by centrifuging, making of very small smears, and counting of those cells which are sufficiently well preserved.

Summary

Four cases are described in which immature myeloid and erythroid cells were found in cerebrospinal fluid in the absence of any disease of the blood. In two cases, a second puncture produced normal fluid.

The presence of these cells is attributed to an accidental vertebral marrow puncture. The most probable site is a lumbar vertebral body, which has an extremely thin cortex on its posterior aspect.

FIG. 5.—Transverse section of a lumbar vertebral body showing the posterior aspect. The cortex here is only about 0·2 mm. thick (× 14).

I should like to thank Mr. Joe Pennybacker and Dr. P. D. Bedford for permission to publish details of their cases; Dr. D. Oppenheimer and Dr. D. B. Brownell for the pathological report on Case 2 and for helpful suggestions; and Dr. A. H. T. Robb-Smith for his advice and criticism.

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TWO HUNDRED AND ONE CASES OF INTRACRANIAL TUBERCULOMA TREATED SURGICALLY

BY

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Of 38,510 patients admitted to the Neurosurgical Clinic of Bucharest during the 23-year period 1935-57, 2,757 were operated upon for expanding intracranial lesions. These included 201 cases of tuberculoma in patients of ages varying from 3 months to 68 years, the highest incidence being recorded under 30 years of age, particularly in the age group below 20 (Table I). The relative frequency of tuberculoma in children is due to the fact that tuberculous infection is relatively commoner during childhood, usually being followed by tuberculoma within a short interval (one month to one year). In patients under 20, the tuberculoma is usually infratentorial, while after the age of 20 it is equally frequent in the infra- and in the supra-tentorial areas.

TABLE I

FREQUENCY OF INTRACRANIAL TUBERCULOMA IN RELATION TO AGE

Age of patients in years	0-10	10-15	15-20	20-30	30-40	40-50	Over 50
Number	15	49	42	71	10	11	3

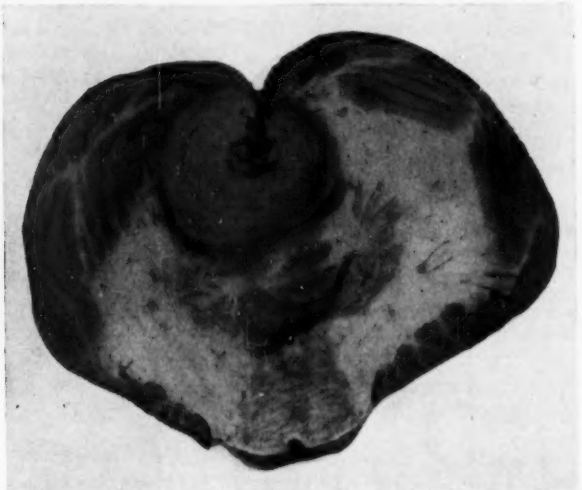

FIG. 1.—Horizontal section of the cerebellum. The tuberculoma is clearly outlined.

Supratentorial tuberculomas are observed more often in men than in women, in a proportion of 3 to 1, whereas those localized below the tentorium are found equally in men and in women.

We met with 32 cases of multiple tuberculoma, in 12 of which the lesions were confined to the cerebellum and in four to the brain-stem; the other 16 had both supra- and infra-tentorial tuberculomas.

The most frequently recorded site (Fig. 1) was in the posterior fossa (67%); 62·5% had a median or paramedian localization within the cerebellum, and 4·5% in the brain-stem. In the cerebrum the most frequent sites were the frontal and parietal lobes, and far less often the temporal lobes, the centrum ovale, the basal ganglia, and only exceptionally, the occipital lobe. The incidence was the same in both hemispheres (Table II).

TABLE II

DISTRIBUTION OF SINGLE AND MULTIPLE TUBERCULOMAS

Number of Tuberculomas	Site		
	Cerebrum	Cerebellum	Brain-stem
169 single tuberculomas	51 (R.26, L.25)	113 (R.53, L.60)	5
32 multiple tuberculomas	16	12	4

Twenty per cent of the total number of tuberculomas were small (less than 15 g.) and these were usually multiple (two to six); 50% of all tuberculomas were of medium size (15 to 20 g.), 27% large (over 20 g.), and 3% were of exceptional size (60 to 100 g.). Clinical symptoms were not proportional to the size of the tuberculoma.

Sixty-six per cent were caseous tuberculomas, 28% were sclerosing, 5·5% were calcified, and one only was described as an abscess. In two-thirds of the cases we noted central necrosis (Fig. 2); in 45% the tuberculoma was in contact with the meninges of the ventricles.

The clinical symptoms were precipitated by infectious diseases, such as measles, whooping-cough, and influenza, in 13% of the cases; by

FIG. 2.—Section through a tuberculoma. Necroses are visible in the central area.

cranio-cerebral injuries in 8%; and by pregnancy, which is liable to aggravate the evolution of tuberculomas in the same way as in cerebral tumours, in 1%.

There was a history of tuberculous infection in 52% of our patients. Pulmonary tuberculosis was noted in the history of 43% of the cases, either in its progressive form (21%) or in the form of residual scars (22%). Chronic extrapulmonary tuberculous lesions were found in 9% of the cases, *viz.*, skin tuberculosis (two cases); lymph node tuberculosis (six cases); ophthalmic tuberculosis (one case); laryngitis (one case); osteo-articular tuberculosis (one case); Pott's disease (three cases); cold abscess (one case); pleuro-peritoneal tuberculosis (one case); and epididymitis (two cases).

In one case the tuberculoma appeared simultaneously with the primary infection. In 21% of the patients with active tuberculous lesions the tuberculoma developed at a late stage. It appeared most frequently (31%) several months or years after the start of the chronic disease. The tuberculoma was apparently primary in 43% of cases, but not infrequently (29%) a source of infection could be traced either within the family or in other contacts. Tuberculoma appeared simultaneously with meningitis in only 3%.

In 20% of our cases, the disease had been progressing for less than three months before the patient was admitted to the clinic; in 30% it had lasted for less than one year; in 45% it had started one to two years before admission; and in 5% between two and three years. In 15% of the cases the general health had been impaired, in 53% the degree of ill-health was moderately severe, and in 32% the general condition was good.

The clinical features of intracranial tuberculoma were found to be related to the site of the lesion and were therefore of the same order as in any other expanding intracranial process. Tuberculomas of the cerebral hemispheres induced a local clinical syndrome in 68% of the cases; in 72% of our patients there were symptoms of intracranial hypertension; 85% of our cases had generalized or focal epileptic fits. In all cases of cerebellar tuberculoma, intracranial hypertension was present, and in 71% of them it was associated with a syndrome of localization (a cerebellar syndrome in 62%, and a syndrome of the ponto-cerebellar angle in 9%). The ponto-cerebellar angle syndrome was associated with a secondary cystic arachnoiditis of the ponto-cerebellar angle, and it was induced by tuberculomas situated in the external third of the cerebellum. In 12% of these cases we noted infratentorial tonic fits.

Tuberculomas situated in the brain-stem always induced local signs and symptoms, whereas raised intracranial tension was delayed or inapparent in 33% (Table III).

TABLE III

CLINICAL FEATURES OF TUBERCULOMAS OF THE CENTRAL NERVOUS SYSTEM

Symptoms	Brain (67 cases)	Cerebellum (125 cases)	Brain-stem (9 cases)
Signs of intracranial hypertension	72%	100%	33%
Symptoms of localization	68%	71%	100%
No symptoms of localization	32%	29%	—
Fits of epilepsy or tonic fits of posterior fossa	85%	12%	—

There are some indications which may be helpful in arriving at a diagnosis of tuberculoma, and they include the patient's history, the clinical examination, and various complementary tests. We are entitled to expect the presence of a tuberculoma when there is a source of tuberculous infection either in the patient himself or in his environment and when there are poor living conditions or debilitating illnesses. Especially is this the case in a young patient in whom a neurological examination reveals intracranial hypertension, with changes in the fundus oculi noted in 94% of cases, either in the form of active papilloedema (51%) or of early secondary optic atrophy (43%), with or without signs of localization, and with a slow course and a tendency towards remission. A diagnosis of tuberculoma can sometimes be made without the presence of pulmonary lesions and with a negative history of tuberculosis.

The diagnosis may be further clarified by means of chest radiographs, tuberculin tests (positive in 25% of tuberculoma cases in children), and simple skull radiographs when calcification will be found in 5·5% of cases (Figs. 3 and 4). Exceptionally (1%) ophthalmoscopic examination may reveal tuberculous lesions. The E.S.R. is less important for it was increased in only 15% of instances.

FIGS. 3 and 4.—Frontal and lateral radiographs of skull, showing characteristic tuberculoma calcifications.

Hypochromic anaemia, however, was frequently encountered, with a relatively high lymphocyte count and a lack of eosinophils. Low-grade fever was noted in 10% of the patients.

Based on a correct interpretation of the personal and family history, as well as on the neurological signs and on the complementary tests, a clinical diagnosis of cerebral tuberculoma could be made in 85% of the cases subsequently operated on.

A differential diagnosis from other intracranial expanding processes has to be made. It is sometimes difficult in those cases of tuberculoma in which there is no evidence of a previous tuberculous infection either in the patient himself or in his family, and in which the complementary tests are negative. The reverse frequently occurs in those instances of cerebral tumour in patients having recently suffered from listlessness or having a history of tuberculosis. It may be difficult to establish a differential diagnosis from occlusive basal meningitis appearing some three weeks to three months after some debilitating disease. The distinction from medulloblastoma of the posterior fossa is easily made, although both diseases are commonly met with in children with manifest signs of intracranial hypertension. In medulloblastoma marked cerebellar and pyramidal signs are often prominent and progress rapidly, while in tuberculoma focal signs are usually only slight.

The prognosis depends upon: (*a*) The general condition; (*b*) the degree and the duration of the intracranial hypertension; (*c*) the presence of other tuberculous lesions in the body (visceral tuberculosis in association with tuberculoma of the nervous system is of serious import); (*d*) the site of the tuberculoma and its relation to the dura mater and the circulation of the cerebrospinal fluid; a tuberculoma of the pons may have a fatal outcome, and tuberculomas which adhere to the dura mater or to the ventricular walls are more liable to induce meningitis; (*e*) the moment of surgical intervention, since an operation at a late stage, when there is severe internal hydrocephalus and cachexia, cannot be expected to yield a good result.

The treatment of brain tuberculoma is both medical and surgical. Before the discovery of streptomycin the excision of the tuberculoma alone or with the surrounding nervous tissue was usually followed by meningitis, so in most cases we were content with simple decompression. Of the 60 patients operated on before the days of streptomycin, there was a general operative mortality of 10% and a subsequent mortality from meningitis of 40%. In radical operations, the surgical mortality added to the mortality from meningitis was as high as 84·5%. All cases of tuberculoma excised from the posterior fossa succumbed through menginitis, while six out of eight cases of excision of supratentorial tuberculoma had a fatal outcome. In palliative operations, without excision of the tuberculoma, there was a mortality of 9% through operation and of 28% through meningitis, with a survival rate of 66%. By decompression and leaving the tuberculoma untouched survival times lasting up to 19 years were obtained (Table IV).

We have operated on and treated with streptomycin 141 cases of supra- or infra-tentorial tuberculoma, with a surgical mortality of 6·3%, a mortality from post-operative meningitis of 6%, and mortality from operation plus meningitis of 12%. Complete recovery was obtained in 88% of the cases (Table V).

Surgical mortality was high in tuberculoma of the brain-stem and of the basal ganglia, as well as in cases with hydrocephalus and cachexia. However, six out of eight patients with tuberculoma of the basal ganglia have been operated on, and four of them are alive. Details of these cases may be found in a paper published elsewhere.

TABLE IV

DELAYED RESULTS RELATED TO THE SURGICAL PROCEDURE EMPLOYED IN 60 CASES OF TUBERCULOMA OPERATED BEFORE THE USE OF STREPTOMYCIN

Surgical Procedure	Site	Results			Percentage of Surgical plus Meningitis Mortality
		Alive	Surgical Mortality	Meningitis Mortality	
Palliative (decompression) (47 cases)	Infratentorial (38 cases)	26(70%)	3(8%)	9(26%)	34
	Supratentorial (9 cases)	5(55%)	1(11%)	3(37·5%)	
Radical (excision) (13 cases)	Infratentorial (4 cases)	—	1(25%)	3(100%)	84·5
	Supratentorial (9 cases)	2(22%)	1(11%)	6(75%)	
Total 60 cases			6(10%)	21(40%)	

Mortality from meningitis was early in six cases and it was due to insufficient treatment in one case; to active visceral tuberculosis in three cases; and to multiple brain tuberculomas, causing repeated attacks of meningitis in two; in another two instances meningitis appeared late, three to six months after the operation, in spite of intensive post-operative treatment.

TABLE V

DELAYED RESULTS IN 141 CASES OF TUBERCULOMA OPERATED ON AND TREATED WITH STREPTOMYCIN

Surgical Procedure	Results		
	Alive	Surgical Mortality	Meningitis Mortality
Palliative (decompression) in brain-stem tuberculomas in 6 cases	2 (33%)	2 (33%)	2 (50%)
Radical (excision) infratentorial in 86 cases	76	5	5
Radical (excision) supratentorial in 49 cases	46	2	1
Total: 141 cases ..	124 (88%)	9 (6·3%)	8 (6%)

In the last 71 patients we had two post-operative casualties and no case of meningitis. All cases (12) of multiple (two to six) cerebellar tuberculoma recovered.

Streptomycin was used by the intramuscular route only in daily doses of 1 g. at a time, up to 80 g., from the time that the temperature and the cerebrospinal fluid became normal. Lately, we have added I.N.A.H. in doses of 10 mg. per kg. body weight.

THE AUGUST (1958) ISSUE

The August (1958) issue contains the following papers:—

Cerebellar Hypoplasia Associated with Systemic Degeneration in Early Life. R. M. Norman and H. Urich.

Clinical and Electroencephalographic Observations in Alzheimer's Disease. F. Letemendia and G. Pampiglione.

Investigations of E.E.G. Findings in Presenile Dementia. D. W. Liddell.

The Centrifugal Pathway for Micturition within the Spinal Cord. P. W. Nathan and Marion C. Smith.

Language Disorder in a Case of Korsakoff's Syndrome. P. R. F. Clarke, Maria Wyke, and O. L. Zangwill.

The Surgical Separation of Siamese Twins Conjoined by the Heads (Cephalopagus Frontalis) Followed by Normal Development. Maitland Baldwin and Anatole Dekaban.

Yawning. Jacques Barbizet.

Ophthalmic Herpes Zoster with Contralateral Hemiplegia. C. Anastasopoulos, K. Routsonis, and C. S. Ierodiakonou.

A Preliminary Report on the Lack of Toxicity of a Preparation of Total Rauwolfia Alkaloids. Homai M. Colabawalla.

The Syndrome of Acute Central Cervical Spinal Cord Injury. Richard C. Schneider, John M. Thompson, and Jose Bebin.

Proceedings of the Society of British Neurological Surgeons: 57th Meeting.

Book Reviews.

A number of copies are still available and may be obtained from the Publishing Manager, British Medical Association, Tavistock Square, W.C.1, price 17*s.* 6*d.*

BOOK REVIEWS

Neuropathology. Ed. by J. G. Greenfield, W. Blackwood, A. Meyer, W. H. McMenemey, and R. H. Norman. (Pp. 640; profusely illustrated. 105*s*.) London: Edward Arnold. 1958.

The production of this book may be regarded as the crowning achievement of the late Dr. Godwin Greenfield. Hitherto, there has been no comprehensive book of reference for neuropathologists in the English language. In German there is volume XIII of the Henke-Lubarsch *Handbuch*, for those with the money to buy it and the patience to use it; otherwise, one has to rely mainly on monographs and papers in scattered journals.

Over half this book is from the hand of Dr. Greenfield, who writes, learnedly and lucidly, on the general pathology of nerve cells and glia, infections, trauma, demyelinating diseases, syringomyelia, cerebello-spinal degenerations, peripheral neuropathies, and the effects of lesions of the skull and spinal column. There is a long and valuable chapter on vascular disease by Professor Blackwood, and an outstanding contribution by Dr. R. M. Norman on malformations and disease of early life. Professor A. Meyer deals with intoxications, metabolic disorders, epilepsy, and the pathology of psychosis. Dr. W. M. McMenemey writes on the organic dementias and diseases of the basal ganglia. The subject of tumours is omitted, as it is to be dealt with in a companion volume edited by Professor D. S. Russell.

The merits of a text-book reveal themselves in use. The present reviewer has been using this one for several months, with profit and pleasure. References are copious, but not too copious; the illustrations are really helpful, and excellently reproduced; and the index is less infuriating than most.

The Sherrington Lectures. Sherrington: Physiologist, Philosopher and Poet. By The Right Hon. Lord Cohen of Birkenhead. (Pp. xiv + 108; illustrated. 17*s*. 6*d*.) Liverpool University Press. 1958.

Lord Cohen was the fourth Sherrington lecturer in the University of Liverpool, and this book consists of his three lectures. His first lecture outlines Sherrington's life. The second lecture on Sherrington as physiologist is informative and well illustrated, and may stimulate the reader to refer to Sherrington's original works, especially "The Integrative Action of the Nervous System". Ground that is less familiar to neurologists is covered by the third lecture on Sherrington as philosopher and poet. Sherrington was a Cartesian dualist and like others was unable to answer the problems of the mind-body relationship. Lord Cohen suggests that the failure of successive generations to deal with these questions is an indication that as they have been asked they are meaningless, and that they must be reformulated before they become answerable. He clarifies this suggestion by apt illustrations.

Chemotherapy of the Central Nervous System. By Henry McIlwain. (Pp. viii + 328; 61 figures, 28 tables. 45*s*.) London: J. & A. Churchill. 1957.

The term chemotherapy suggests the use of drugs to combat infection. Professor McIlwain uses the word in a much wider sense and his text is the vast range of chemical compounds which influence the activity of the central nervous system. It is written primarily from the standpoint of a chemist and the inter-relations between various drugs and the principles which governed their development are most lucidly described. The biological meaning which can be extracted from a knowledge of their molecular structure is thereby illustrated.

The work of the past is extensively described and much out-of-the-way information is included. It is interesting to note the occurrence of names which are better known in other branches of medicine. Von Mering, for example, who with Minkowski discovered the role of the pancreas in blood sugar regulation, collaborated with Emil Fischer in work which resulted in the introduction of the barbiturates. Sigmund Freud with Kollar was responsible for the introduction of cocaine to ophthalmology.

This is an excellent book. It is broad in scope and the simple fact that several hundred active substances are considered illustrates the scope of neurological therapy.

Eisen, Kupfer und Eiweiss am Beispiel der Leberkrankheiten. By J. Lange; Foreword by Prof. Paul Martini. (Pp. viii + 89; 37 figures. DM 13.50.) Stuttgart: Georg Thieme. 1958.

This small monograph gives a valuable account of the metabolism of iron and copper, with special reference to research on haemochromatosis and hepato-cerebral degeneration. A list of over 400 references is provided.

Clinical Neuro-ophthalmology, 2nd ed. By Frank B. Walshe. (Pp. xvi + 1294; illustrated. 231*s*.) London: Baillière, Tindall & Cox. 1957.

The scope of neuro-ophthalmology is sometimes taken to include only the oculomotor nerves and the pathways from eye to visual cortex. These subjects, however, occupy only a small proportion of this massive book and the remainder is devoted to a wide variety of neurological disorders which may be associated with ophthalmic abnormalities. This involves sections on such diverse subjects as the presenile dementias, osteogenesis imperfecta, Arnold-Chiari deformity, and the Guillain-Barre syndrome. On debatable subjects the various points of view are stated individually and this is followed by the author's summing up. Most points are illustrated by case

records from the author's experience, and these are often given with engaging candour. The book can be thoroughly recommended to neurologists, and it is to be feared that few neurologists are as expert in ophthalmology as Dr. F. B. Walshe is in neurology.

Psychosomatic Ophthalmology. By T. F. Schlaegel, Jr., with the collaboration of Millard Hoyt. (Pp. x + 502 + Index. 88s.) London: Baillière, Tindall & Cox. 1957.

The author is a teacher and practitioner of ophthalmology in the University of Indiana and also a qualified psychiatrist. He believes that " a hundred per cent " of eye cases involve emotional conflict and as a corollary, " the true psychosomatic approach " is necessary for proper treatment. This approach is in the prevailing American dynamic tradition. The author believes that the eye may represent symbolically either the male or female genitals (the penis, for example, being represented by " the hypothetical beam emanating from the pupil "). The entire face may also represent the male genital area, the eyebrows representing the pubic hair, the nose the penis, and the eyes, in this particular analogy, the testes. The forehead can be used as an equivalent for the eye, and symbolize the same anatomical regions. These hypotheses are buttressed by evidence from Greek mythology and the citation of some curious practices of the Austrian peasantry. If one accepts these hypotheses the door would seem to be wide open for a plethora of fantasy, but the author does not grasp his opportunity and the rest of the book consists mainly of hysteria discussed on an anatomical basis, with chapters on neurology, dermatology, headache, and general medicine in so far as they affect the eye.

Clinical Neurosurgery. Vol. 4. (Pp. x + 140 + Index; illustrated. 56*s*.) London: Baillière, Tindall & Cox. 1957.

This small volume contains the proceedings of the Sixth Annual Meeting of the Congress of Neurological Surgeons held in Chicago in November, 1956. It is dedicated to Dr. Wilder Penfield, O.M., of Montreal, but apart from two papers by Dr. Penfield together with his bibliography and a short biography, it is really a symposium on pituitary surgery. The first of Dr. Penfield's contributions is an account of the life and times of Hippocrates based upon material gained during his two visits to the island of Cos. The second is some thoughts on the function of the temporal cortex, and summarizes his observations on perceptual illusions and experimental hallucinations published in other papers. It contains two statements that, if confirmed by a larger documentation, are new and important, *viz*., that auditory illusions and the feeling of fear may be produced by discharges in the temporal cortex of either side, whereas visual illusions and *déjà vu* sensations are generally produced by discharges in the temporal cortex of the non-dominant hemisphere.

Six papers by various authors portray various aspects of pituitary surgery. The first three by Drs. C. W. Rucker, J. D. Camp, and J. G. Love—all of the Mayo Clinic—deal respectively with ophthalmological, radiological, and operative aspects. They follow more or less standard teaching and indicate that at their clinic most patients with failing vision are submitted to surgery. Then follows a somewhat provocative article by the late Dr. Gilbert Horrax reporting the results in 95 patients treated at the Massachusetts Institute of Technology with a two-million volt radiotheraphy apparatus using a rotational method of application and delivering a tumour dose of 4,000 r. The results are compared with his earlier experiences at the Lahey Clinic of operative treatment with or without the more conventional forms of deep *x*-ray therapy. He found that with the two-million volt apparatus only 12% of patients with impaired vision failed to respond to radiotherapy compared with 58% previously. Admittedly the follow-up period of these more recent cases is only one to six years, but the results indicated that a more prolonged trial of this new therapy is necessary.

The two concluding papers discuss succinctly the treatment of metastatic breast cancer by surgical hypophysectomy. The first of these by Dr. B. S. Ray describes the surgical technique and summarizes the operative results, while the last by Dr. O. H. Pearson discusses the physiological affects of the operation. A feature of all the papers is the edited report of the discussions from the floor. The monograph can be commended to all who want a short account of the present status of pituitary surgery.

Die Prognose der Wirbelsaulenleiden: Eine berufsprophylaktische Betrachtung. By J. E. W. Brocher. (Pp. viii + 67; 33 figures. DM. 12.80.) Stuttgart: Georg Thieme. 1957.

In this study the author discusses various congenital, degenerative, and inflammatory anomalies of the spine, with special reference to occupational prophylaxis. Special emphasis is laid on Scheuermann's disease, spina bifida, butterfly vertebra, and haemangioma of the spine.

There is no doubt that these vertebral anomalies may represent risks for employment in certain occupations, and the author rightly draws attention to the great value of clinical, as well as *x*-ray, examinations for the selection of suitable candidates for certain industries and professions, such as physical gymnastics, nursing, and also for recruiting for military service.

A Study of Major Psychoses in an English County. Maudsley Monograph No. 3. By Michael Shepherd. (Pp. 159 + 28 histograms. 25*s*.) London: Institute of Psychiatry and Chapman & Hall. 1957.

It is customary and reasonable to demand that the natural history of a disease should be determined before any attempt is made to assess the value of therapeutic interference. Neglect of this requirement has led to faulty conclusions, notably in regard to the treatment of mental illness. The natural history of mental illness is, however, very hard to determine, not least because its ascertainment and its forms and frequency depend on social factors. The extent of this dependence is documented by the thorough and sophisticated Maudsley

monograph by Dr. Shepherd. Examining the patients admitted to a county mental hospital in the two triennia 1931-33 and 1945-47, he records striking changes. In the later period more patients were admitted (but the first admission rate was lower and the readmission rate higher than in the earlier period); the outlook for patients with affective disorder, especially women, was better; and even patients with organic and senile psychoses spent less time in hospital. Dr. Shepherd interprets these changes as being due to the impact of social and legislative measures, the admission of patients at an earlier stage of their illness or with a more responsive form of illness, and the introduction of new forms of treatment; the last of these, however, is not, in his reasoned view, the dominant factor in reducing the duration of stay for patients with non-organic psychoses. There have been very few studies such as this: they are needed, for it casts light upon many controversial questions that are of moment not only to the psychiatrist but also to the public health administrator and the sociologist.

Integrating the Approaches to Mental Disease. Two conferences held under the auspices of the Committee on Public Health, New York Academy of Medicine. Edited by H. D. Kruse. (Pp. xvi + 393.) London: Cassell. 1958.

Future historians of psychiatry may label this the " palaver period ". Never before have psychiatrists come together so often with experts in other branches of knowledge—psychology, sociology, anatomy, physiology, genetics, biochemistry, anthropology, statistics, and neurology—to discuss each other's ideas, methods, and joint potentialities. These conferences, bewilderingly discursive and ragged, nevertheless provide those who attend them with stimulating fresh concepts and widen their horizon. Whether the transcripts of the discussion, which it is now customary to publish, serve the same excellent purpose for readers is extremely doubtful. At worst they excite surprise that such able men can on occasion be so muddled or one-eyed, and at best they confirm the suspicion that talk about complex unresolved problems is likely to be at cross purposes unless the people engaged in it have some common ground, set fourth clearly at the outset, and understand each other's private language.

Forty-eight representatives of psychiatry and other subjects attended the two New York conferences here reported. All but six of the participants were American or Canadian; 23 were psychiatrists. At the first conference the principles and bases of four major approaches to mental disease—organic, experimental psychological, psycho-analytical, and social—were presented, and areas of agreement sought. None of the exponents claimed exclusive value for the approach he preferred in his research or his practice. In the second conference the psychodynamic approach was clearly seen to be least reconcilable with the organic or experimental viewpoint; difficulties of communication and diversity of method were chiefly repsonsible for this lack of common ground.

The reader of this handsomely produced volume oscillates between admiration for the intelligent, exceptionally well-informed and perceptive contributions made when the participants were dealing with their own field of knowledge and dismay at the wordy labyrinths into which they wandered or scurried when they came up against age-old problems (such as the permanence of values, or the essential nature of the scientific method) or ventured into assumptions and arguments concerning subject matter unfamiliar to them. The problems of interdisciplinary research are probably better solved ambulando than by discussion, even between such notable scientists and clinicians as were assembled at these two conferences.

L'Enfant Inadapté: Rôle médico-social du Médecin. By L. Michaux and D. J. Duché. (Pp. 316. Fr.fr. 3,600.-.) Paris: G. Doin. 1957.

This book is one of a series of therapeutic manuals. In a long and interesting preface Professor Heuyer, the doyen in France of the psychiatry of childhood, explains that schoolteachers and psychologists have made inadmissible claims to diagnose and treat maladjusted children, and he elaborates the grounds on which these responsibilities should fall predominantly on the clinician, working in association with teacher and psychologist. The medical standpoint which he commends is conspicuous in Professor Michaux and Dr. Dupre's manual. It is written in the manner of a simple textbook: statements tend to be dogmatic and unqualified, argument is eschewed, and there are no detailed references to the literature of the subject. It is, however, clearly arranged and presented. The therapeutic guidance offered is mostly terse and empirical.

Le Delirium Tremens. By R. Coirault and H. Laborit. (Pp. 140; 21 figures. Fr. frs. 1,200.-.) Paris: Masson. 1956.

Delirium tremens, as part of the general problem of alcoholism, is a not uncommon condition in France. It has been the subject of considerable clinical and biochemical study in the past decade. This small monograph reviews the work of its senior authors particularly in the biochemical field. They say in the preface " L'ion K dominera ce travail " and in conclusion state that a trial of changes in potassium ion distribution —lowered concentration in blood and urine and raised concentration in cells—constitutes a basic mechanism in delirium tremens. This abnormality they can readily correct by cortisone or better still by 21-hydroxy-pregnandione-sodium succinate. If their clinical results are correctly observed and reported it would certainly seem that these authors have found a rapid and dramatic cure for acute delirium tremens.

Pain and Pleasure. By Thomas S. Szasz. (Pp xvi + 301. $5.50.) New York: Basic Books. 1957.

This book stresses a psychoanalytical theory of pain, but this becomes hardly understandable when an attempt is made to explain the appearance of a phantom limb pain as " a return of the denied " (p. 159). There is, in fact, conclusive evidence that the neuronal discharge which provokes phantom sensations usually originates in the nerves of the stump, and not in the " psychic structure ", wherever that may be.

BOOKS RECEIVED

(Review in a later issue is not precluded by notice here of books received.)

Polymyositis. By John N. Walton and Raymond D. Adams. (Pp. x+170; 47 figures. 32*s*. 6*d*.) Edinburgh and London: E. & S. Livingstone. 1958.

Homosexuality: Its Nature, Causation, and Treatment. By Clifford Allen. (Pp. 143. 15*s*.) London: Staples Press. 1958.

The Patient Speaks. By Harold A. Abramson. (Pp. xx+237. $3.50.) New York: Vantage Press. 1958.

German-English Glossary of Neurophysiology. Edited by R. M. Morrell. (Pp. 181. $7.50.) New York: Consultants Bureau, Inc. 1958.

Thinking: An Experimental and Social Study. By Sir Frederic Bartlett. (Pp. 203. 18*s*.) London: Allen & Unwin. 1958.

Chronic Schizophrenia. By Thomas Freeman, J. L. Cameron, and Andrew McGhie. (Pp. x+158. 21*s*.) London: Tavistock Publications. 1958.

Hysterie, Reflex und Instinkt. By Ernst Kretschmer. (Pp. viii+148. DM 12.80.) Stuttgart: Georg Thieme. 1958.

Elektroencephalographische Studien bei Hirntumoren. By Rudolf Hess; Foreword by H. Krayenbuhl. (Pp. iv+100; 8 figures. DM 19.70.-.) Stuttgart: Georg Thieme. 1958.

Opotalamo e Neuricrinia. By Gian Giacomo Cavalca. (Pp. xiii+207+Index; 73 figures. No price given.) Bologna: Lianio Cappelli. 1957.

Stuttering: A Psychodynamic Approach. By Dominick A. Barbara. (Pp. 225. 25*s*.) London: Hutchinson. 1958.

Communication, Organization, and Science. By Jerome Rothstein; Foreword by C. A. Muses. (Pp. xcvi+110. $3.50.) Indian Hills, Colorado: The Falcon's Wing Press. 1958.

Neuritis, Sensory Neuritis, Neuralgia. A Clinical Study with Review of the Literature. By R. Wartenberg; Foreword by W. Harris. (Pp. xii+444. 68*s*.) London: Oxford University Press. 1958.

Die Hirngeschwülste in biologischer und morphologisher Darstellung, 3rd ed. By K. J. Zülch. (Pp. vii+249; 102 figures. DM 27.80.) Leipzig: Johann Ambrosius. 1958.

The Student Life: The Philosophy of Sir William Osler. Edited by Richard E. Verney; Foreword by John Bruce and Alec H. Macklin. (Pp. xiii+214. 15*s*.) Edinburgh and London: E. & S. Livingstone. 1957.

Maladies de L'Oreille Interne et Oto-Neurologie. By M. Aubry and P. Pialoux. (Pp. 706; 197 figures. Fr. fr. 9,900.-.) Paris: Masson. 1957.

L'Hydrocéphalie du Nourrison. By Marc-Richard Klein in collaboration with Mme. L. Delegue, Mlle. J. Scharff, and Mme. E. Bargeton; Foreword by Marcel Fevre. (Pp. 136; 37 figures. Fr. fr. 1,600.-.) Paris: Masson. 1958.

Fundamentals of Neurology, 3rd ed. By Ernest Gardner. (Pp. xi×388; 154 figures. 40*s*.) Philadelphia and London: W. B. Saunders. 1958.

A New Approach to Schizophrenia. By Julius I. Steinfeld. (Pp. 159. 21*s*.) London: Hutchinson. 1958.

Homosexuality, Transvestism and Change of Sex. By Eugene de Savitsch. (Pp. viii+120. 12*s*. 6*d*.) London: Heinemann. 1958.

Autonomic Dyspraxia: An Hypothesis for the Mechanism of Psychosis, Neurosis and Psychosomatic Disease. By Brian G. Haynes. (Pp. viii+122. 15*s*.) London: H. K. Lewis. 1958.

The Cerebrospinal Fluid: Production, Circulation, and Absorption. A Ciba Foundation Symposium. Edited by G. E. W. Wolstenholme and Cecilia M. O'Connor. (Pp. xii+335; 141 figures. 50*s*.) London: J. & A. Churchill. 1958.

Foundations of Neuropsychiatry, 6th edition revised and enlarged. By Stanley Cobb. (Pp. ix+305+Index. 40*s*.) London: Baillière, Tindall & Cox. 1958.

Attempted Suicide: Its Social Significance and Effects, Vol. 4 (Maudsley Monographs). By E. Stengal and Nancy G. Cook. (Pp. 136. 25*s*.) London: Chapman & Hall. 1958.

Viral Encephalitis. A Symposium. Fifth Annual Scientific Meeting of the Houston Neurological Society, Texas Medical Center, Houston, Texas. Compiled and edited by William S. Fields and Russell J. Blattner. (Pp. ix+225; illustrated. 52*s*. 6d.) Oxford: Blackwell Scientific Publications; Springfield, Illinois: Charles C. Thomas. 1958.

The Sherrington Lectures V. **The Excitable Cortex in Conscious Man.** By Wilder Penfield. (Pp. ix+43; 15 figures. 10*s*. 6*d*.) Liverpool University Press. 1958.

Butterworths Medical Publications 1958. (Pp. 52; illustrated. Free.) London: Butterworth. 1958.

Topics in Psychiatry. Edited by T. Ferguson Rodger, R. M. Mowbray, and J. R. Roy. (Pp. x+265. 20*s*.) London: Cassell. 1958.

Biology of Neuroglia. Edited by William F. Windle. (Pp. xiv+340; 78 figures. 63*s*.) Oxford: Blackwell Scientific Publications; Springfield, Illinois: Charles C. Thomas. 1958.

Carbon Dioxide Therapy, 2nd ed. Edited by L. J. Meduna. (Pp. xii+541; graphs and tables. 110*s*.) Oxford: Blackwell Scientific Publications; Springfield, Illinois: Charles C. Thomas. 1958.

Autonomic Imbalance and the Hypothalamus. By Ernst Gellhorn. (Pp. xiv+300; 101 figures. 68*s*.) Minnesota University Press (London: Oxford University Press). 1958.

External Collimation Detection of Intracranial Neoplasia with Unstable Nuclides. By G. M. Shy, R. B. Bradley, and W. B. Matthews, Jr., with a chapter on *Scintillation Spectrometry* by J. E. Francis, P. R. Bell, and C. C. Harris. (Pp. vii+144; illustrated. 30*s*.) Edinburgh and London: E. & S. Livingstone. 1958.

The Facts of Mental Health and Illness. New (2nd) edition fully revised. By K. R. Stallworthy. (Pp. 218. 22*s*. 6*d*. New Zealand price.) Christchurch, N.Z.: N. M. Peryer. 1958.

Amphetamine Psychosis (Maudsley Monographs No. 5). By P. H. Connell. (Pp. 133. 21*s*.) London: Chapman & Hall. 1958.

Thudichum—Chemist of the Brain. By David L. Drabkin. (Pp. 309; 52 figures. 40*s*.) London: Oxford University Press. 1958.

A Primer of Cerebral Palsy. By Joseph D. Russ and Hyman R. Soboloff. (Pp. viii+77; 16 figures. 30*s*.) Oxford: Blackwell Scientific Publications; Springfield, Illinois: Charles C. Thomas. 1958.

Ein binauraler Hörsynthese-Test zum Nachweis zerebraler Hörstörungen. By J. Matzker; Foreword by H. Leicher. (Pp. x+117; 46 figures. DM 19.80.) Stuttgart: Georg Thieme. 1958.

A Ciba Foundation Symposium on the **Neurological Basis of Behaviour** in commemoration of Sir Charles Sherrington, O.M., G.B.E., F.R.S., 1857-1952. Edited by G. E. W. Wolstenholme and Cecilia M. O'Connor. (Pp. xii+400; illustrated. 52*s*. 6*d*.) London: J. & A. Churchill. 1958.

Le Syndrome Tétanie. By Th. Alajouanine, F. Contamin, and H. P. Cathala. (Pp. 279; 29 figures.) Paris: J. B. Baillière 1958.

La Physiologie et la Physiopathologie du Cervelet. By A. Kreindler and M. Steriade; Foreword by P. Mollaret. (Pp. 308; 87 figures. Fr. fr. 3,200.-.) Paris: Masson. 1958.

Le Syndrome de Guillain-Barré et les polyradiculonévrites aiguës avec dissociation albumino-cytologique dans la liquide céphalorachidien. By R. Coirault, A. Larcan, and P. Davidou; Foreword by P. Garcin. (Pp. 200. Fr. fr. 2,000.-.) Paris: Masson. 1958.

Psychotherapy by Reciprocal Inhibition. By Joseph Wolpe. (Pp. xiv+239. 40*s*.) London: Oxford University Press. 1958.

Thérapeutique Neurologique et Psychiatrique, 2nd edition entirely revised. By Paul Cossa in collaboration with H. Bougeant, J. Boudouresques, J. Duplay, E. Le Coq, J. Postel, and R. Rivoire. (Pp. 610. Fr. fr. 4,800.-; bound 5,800.-.) Paris: Masson. 1958.

Theory of Psycho-Analytic Technique. By Karl A. Menninger. (25*s*.) London: Imago Publishing Co. 1958.

Diagnostica Psichiatrica, Parte Speciale. By Agostino Rubino; Foreword by Prof. V. H. Buscaino. (Pp. xiv+443; 99 figures. L. 5,500.-.) Naples: Libraria V. Idelson. 1958.

Psychopathic Personalities, 9th ed. By Kurt Schneider (translated by M. W. Hamilton); Foreword by E. W. Anderson. (Pp. xiv+163. 18*s*.) London: Cassell. 1958.

Die beginnende Schizophrenie. By K. Conrad. (Pp. viii+165. DM 19.80.) Stuttgart: Georg Thieme. 1958.

The Waking Brain. By H. W. Magoun. (Pp. viii+138; 55 figures. 36*s*.) Oxford: Blackwell Scientific Publications; Springfield, Illinois: Charles C. Thomas. 1958.

Clinical Neuroanatomy, Neurophysiology and Neurology: with a Method of Brain Reconstruction. By Louis Hausman. (Pp. xxv+522; 9 plates. 73*s*. 6*d*.) Oxford: Blackwell Scientific Publications; Springfield, Illinois: Charles C. Thomas. 1958.

Differentialdiagnose Neurologischer Krankheitsbilder. Edited by G. Bodechtel. (Pp. xxviii+975; 533 figures. DM 120.-.) Stuttgart: Georg Thieme. 1958.

The Physical Foundation of Biology. By Walter M. Elasser. (Pp. 219; 16 figures. 30*s*.) London: Pergamon Press. 1958.

The Brain and Human Behaviour. Proceedings of the Association for Research in Nervous and Mental Disease, Vol. XXXVI. Edited by Harry C. Solomon, Stanley Cobb, and Wilder Penfield. (Pp. xi+564; illustrated. 120*s*.) London: Baillière, Tindall Cox. 1958.

Clinical Examination of the Nervous System, 11th ed. By G. H. Monrad-Krohn. (Pp. xx+466; 173 figures. 40*s*.) London: H. K. Lewis. 1958.

L'Hypophysectomie dans le Traitement du Cancer. By J. Le Beau; Foreword by Prof. Marcel Perrault. (Pp. 126; 17 figures. Fr. frs. 1,800.-.) Paris: G. Doin. 1958.

Psychopharmacology: Pharmacologic Effects on Behaviour. Edited by Harry H. Pennes. (Pp. xiv+362; 35 figures. 60*s*.) London: Cassell. 1958.

The Psychiatric Hospital as a Small Society. By William Caudell. (Pp. xxiii+406; illustrated. 52*s*.) Harvard University Press (London: Oxford University Press.) 1958.

Diseases of the Nervous System, 9th ed. By Sir Francis Walshe. (Pp. xvi+373; 58 figures. 30*s*.) Edinburgh and London: E. & S. Livingstone. 1958.

Cure de Sommeil Collective et Psychothérapie de Groupe. By Henri Faure; Foreword by Prof. Henri Ey. (Pp. 272; 5 figures. Fr. fr. 2,500.-.) Paris: Masson. 1958.

Head Injuries. Compiled by E. S. Gurdjian and J. E. Webster. (Pp. 482; $14.-.) Boston: Little, Brown & Company. 1958.

Correction. In the paper "Investigations of E.E.G. Findings in Presenile Dementia", published in August, 1958, (*J. Neurol. Neurosurg. Psychiat.*, **21**, 173) we regret that the descriptions of records (Figs. 2 and 3) have been interchanged.

Foundations' Fund for Research in Psychiatry

The next deadline for the submission of completed applications for research fellowships in psychiatry, psychology, sociology, neurophysiology, and other sciences relevant to mental health is January 15, 1959.

The next deadline for receipt of applications for research grants-in-aid is December 10, 1958. Interested persons are invited to write for details to: Foundations' Fund for Research in Psychiatry, 251 Edwards Street, New Haven 11, Connecticut.

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